Health-Related Quality of Life in Patients Treated With Antiretroviral Therapy Only Versus Chemotherapy and Antiretroviral Therapy for HIV-Associated Kaposi Sarcoma: A Randomized Control Trial

abstract

Purpose In sub-Saharan Africa, Kaposi sarcoma (KS) is the most common HIV-associated cancer. KS causes substantial morbidity, and treatment goals should emphasize quality of life (QOL). Antiretroviral therapy (ART) is indicated, and early chemotherapy significantly improves tumor regression. The effect of ART alone or with chemotherapy on QOL in treatment-naïve South Africans with HIV-associated KS was assessed.

Methods KAART (Kaposi Sarcoma AIDS Anti-Retroviral Therapy) is a randomized, controlled, open-label trial of ART versus ART plus chemotherapy. Crossover between arms was allowed for patients with progressive disease. Eighty-nine percent of patients had advanced tumor burden. Within KAART, QOL measured by European Organization for Research and Treatment of Cancer-QLQ-C30 questionnaire evaluated functional and symptom domains and global QOL. Intragroup changes between baseline and month 12 (Wilcoxon rank sign test), changes between the arms (Mann-Whitney test), and the relationship between responses, determined by AIDS Clinical Trial Group criteria and QOL measures (Kruskal-Wallis test), were evaluated. *P* values < .01 were considered significant.

Results QOL information was available for 111 of 112 patients. Significant improvements over 12 months were seen in global health status and functional scales (emotional, cognitive, and social scales; not physical and role function). Most symptom scales (fatigue, pain, dyspnea, insomnia, appetite, diarrhea, and constipation) also showed significant improvement. There were no statistically significant changes between arms in intention-to-treat analysis. Patients showing a response to the tumor (complete or partial) reported significantly increased global QOL (*P* < .001), pain relief, and improved role functioning. Adherence, adverse events, HIV viral load, and CD4 count did not correlate with global QOL.

Conclusion African patients with HIV-associated KS derive a significant benefit in QOL from ART and tumor regression.

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INTRODUCTION

Kaposi sarcoma (KS) is a multifocal spindle cell tumor caused by Kaposi sarcoma herpesvirus (KSHV, also known as human herpesvirus-8).[1] KS is strongly associated with HIV and related immune dysregulation. Its burden increased dramatically with the HIV epidemic in KwaZulu-Natal, South Africa, with a 30-fold increase in the age-standardized incidence rates.[2] Although the introduction of antiretroviral therapy (ART)

decreased the incidence of HIV-associated KS in resource-replete countries with relatively low KSHV seroprevalence, the absolute benefit is less clear in resource-limited areas with high KSHV seroprevalence.[3] KS remains the most common HIV-related cancer in sub-Saharan Africa, with an estimated incidence greater than 130 per 100,000 person-years among people receiving ART.[4] Although many people with HIV-associated KS are managed with ART alone, the addition of chemotherapy is needed in patients

with advanced disease. Despite therapy, mortality remains high.[5] Patients with HIV-associated KS have a more than three-fold increased risk of dying after initiation of ART compared with HIV-infected patients without KS.[6]

Increasing overall survival in HIV-associated KS is an essential goal of treatment. KS may also cause substantial morbidity; therefore, therapies are aimed at maximal and durable tumor regression and meaningful palliation of symptoms.[7] Data on the effect of ART with and without chemotherapy on quality of life (QOL) are crucial when evaluating treatment programs for African patients with HIV-associated KS, because resources for therapy are limited and QOL outcomes may direct cost-effective therapy. Health-related QOL assessments have become an important tool in assessing trial data, because user satisfaction, over and above investigator assessment, is essential. Within KS clinical studies, QOL outcomes are an important adjunct to measurements of clinical response by AIDS Clinical Trials Group (ACTG) criteria and provide important information about the effects of different therapies in HIV-associated KS.

To date, only one QOL study has been conducted in African patients with HIV-associated KS. This was before the availability of ART, and it compared the efficacy of supportive care versus three KS treatment interventions (oral etoposide, a three-drug chemotherapy regimen, and radiotherapy) in Zimbabweans.[8] Additional studies performed in the United States and Europe evaluated the effects of chemotherapy (etoposide,[9] paclitaxel,[10] pegylated liposomal doxorubicin versus doxorubicin, bleomycin, and vincristine[11] and paclitaxel versus pegylated liposomal doxorubicin[12]) on multiple domains of QOL but did not compare these to ART alone. To our knowledge, the current study is the first to evaluate the effects of ART, with or without chemotherapy, on QOL in HIV-associated KS. We hypothesized that early administration of chemotherapy would be associated with improved QOL over that of ART alone. Differences in QOL domains between treatment arms, as well as associations between QOL and several clinical parameters (CD4 counts, HIV viral load, adherence, and adverse events) were also assessed.

METHODS

Patients

KAART (Kaposi Sarcoma AIDS Anti-Retroviral Therapy) was a randomized, controlled, open-label trial evaluating ART alone or in combination with early chemotherapy in South African patients in Kwa-Zulu Natal with HIV-associated KS. The study, conducted between 2003 and 2009, consisted of 62 women and 50 men not previously treated with ART or KS-specific therapies. Patients were staged into good or poor risk according to modified ACTG criteria and then randomly assigned to receive ART or ART and chemotherapy by a four-digit computer-generated code. Chemotherapy generally consisted of doxorubicin, bleomycin, and vincristine, and in participants randomly assigned to early chemotherapy, it was administered within 4 weeks of the initial visit. Those with progressive disease in the ART-alone arm were allowed to cross over. Complete details of study methodology have been previously published.[13] This study was approved by the Nelson R. Mandela School of Medicine institutional review board and listed on ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT00380770). All participants provided written informed consent.

Assessments

The cancer-specific European Organization for Research and Treatment of Cancer 30-item QOL questionnaire (EORTC QLQ-C30) was used[14] to assess QOL prospectively in all patients at baseline (pretreatment) and once every 3 months until month 12 (trial completion). Permission to use this instrument was given by the EORTC QLQ division.[15] The questionnaire was translated into isiZulu by linguists fluent in both languages, so that the original meaning was retained.

The QLQ-C30 is a questionnaire developed to assess the quality of life of patients with cancer in clinical trials and has been used in more than 9,000 studies. It is a self-reported, 30-item questionnaire composed of multi-item scales (five functional, three symptom, and a global health status [GHS] scale) and six single-item measures used to evaluate QOL domains.[16] All QOL domains range in score from 0 to 100. High scores for a functional or GHS scale represented a high QOL, whereas a high score for a symptom scale or item represented a high level of

symptoms or problem associated with a negative impact on QOL.

KS responses were graded as complete, partial, stable, and progressive disease using ACTG criteria.[17] ART adherence was assessed by a study nurse using a validated 7-day self-report questionnaire at week 2, week 4, and once per month thereafter.[18] Mean adherence over the course of the study was calculated as a percentage (greater than 95% was excellent, 80% to 94% was good, and less than 80% was poor). Adverse events (AEs) were graded using Division of AIDS criteria. Grade 3 to 5 AEs were considered serious (SAEs). Cumulative adverse events were the total number of AEs experienced during the trial.

Statistical Analysis

The primary objective of the study was to evaluate changes in QOL over time and compare changes between arms. Secondarily, associations between KS response, clinical parameters, and select QOL domains were evaluated. Nonparametric testing was used to perform baseline comparisons as well as inter- and intragroup comparisons over time, and results were represented as medians. We performed an intention-to-treat comparison of each scale between the two groups at baseline (Mann-Whitney test), intragroup changes between baseline and month 12 QOL scores (Wilcoxon rank sign test), and changes between baseline and month 12 QOL scores between the two groups (Mann-Whitney test). Relationship between tumor response (KS response) and pain and role functioning (Mann-Whitney test), as well as KS response and GHS (Kruskal-Wallis test), were evaluated. Given multiple comparisons, P values $< .01$ were considered statistically significant, $.01 < P < .05$ represented important trends, and $.05 \leq P \leq .1$ represented possible trends.

The effects of time receiving therapy and several clinical parameters on the GHS and domains where there was at least a possible trend of difference between arms ($P \leq .1$) were evaluated. Log_{10} GHS was used as the dependent variable at four time points (months 3, 6, 9, and 12) in a generalized linear model under the Gaussian family of distributions, with an identity link and robust clustered SEs to adjust for the repeated within-subject measures. Independent variables included parameters hypothesized to be important

determinants of GHS, including: treatment arm, time in study, an interaction variable for time in a treatment arm, and clinical response of KS to treatment (at months 3, 6, 9, and 12), to demonstrate the adjusted influence of these factors on GHS over time.

RESULTS

Patient Characteristics

In the KAART study, 59 patients were randomly assigned to ART alone and 53 were randomly assigned to ART plus chemotherapy. Median age was 33 years in the ART-alone arm and 34 years in the chemotherapy arm. Sixty-nine percent of participants were urban from Durban, and 31% were from rural Kwa-Zulu Natal. At baseline, 89% of participants randomly assigned to ART alone had a high tumor burden (T_1), and 41% had "B" symptoms or a history of opportunistic infection; 94% of participants randomly assigned to chemotherapy had a high tumor burden (T_1), and 38% had B symptoms or a history of opportunistic infection; median CD4+ T-cell count was 136 cells/μL in the ART-alone arm and 192 cells/μL in the chemotherapy arm (Data Supplement). Twenty-two percent of patients randomly assigned to ART alone crossed over to receive chemotherapy, and 28% of patients randomly assigned to early chemotherapy received ART alone. ART adherence was reported as excellent in 67 (60%), good in 33 (30%), and poor in 11 (10%), with no difference between arms. At 12 months, the overall response (partial or complete response) was significantly improved in the arm randomly assigned to receive chemotherapy, with 39% observed in the ART-alone arm and 66% in the chemotherapy arm. Overall survival at 12 months was 77%, with no significant difference between arms. Of the 112 participants, 111 had QOL information; one of the patients did not complete the baseline questionnaire and subsequently defaulted follow-up.

At baseline, 105 (94.6%) questionnaires were available for analysis, 92 (82.9%) at month 3, 87 (78.4%) at month 6, 81 (73%) at month 9, and 77 (69.4%) at month 12 (Fig 1). At baseline, GHS ($P = .005$) and role function ($P = .001$) were significantly elevated in the ART-alone arm, whereas pain ($P = .017$) and financial problems ($P = .018$) showed a borderline increase in the chemotherapy arm, despite random assignment (Table 1).
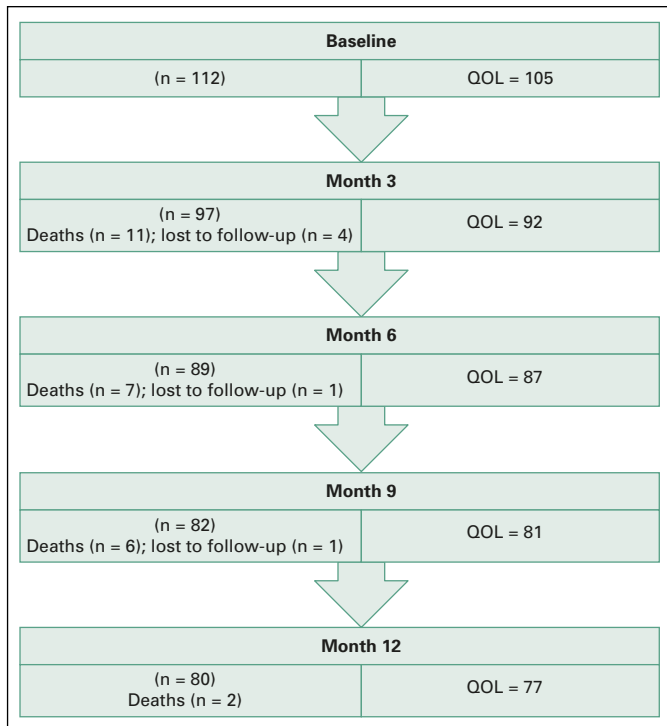
Fig 1. Participant flow diagram and available quality-of-life data (QOL) at each visit.

role function, as well as pain (score = 50) and financial difficulties (score = 100) were the most common domains adversely affected by disease status. Participation in KAART lead to improved QOL across most measured domains. Median GHS was 50 at baseline, improving significantly at month 12 to 67. Significant improvements in functional scale scores were seen in emotional, cognitive, and social subscales. Physical function, which was high at baseline (score = 87), only marginally improved (score = 93; *P* = .158), and role function did not increase in the overall group. Most symptoms improved significantly in patients over time, including fatigue, pain, insomnia, diarrhea, constipation, dyspnea, and appetite. Nausea, which was a less common symptom at baseline (score = 0), improved, although changes were only of marginal statistical significance (*P* = .032). Financial problems showed the greatest decrease.

EORTC QLQ-C3O: Comparison Between the Arms

In an intention-to-treat analysis, we evaluated difference in improvement between arms (Table 2). Statistically significant intra-arm improvement from baseline to completion of treatment was demonstrated in both treatment groups

EORTC QLQ-C3O: Changes Over 12 Months

Figure 2 provides EORTC QLQ-C30 score in the overall study population, pretreatment, and at the completion of the trial. Poor GHS and

Table 1. Baseline Quality-of-Life Domains by Treatment Arm

QOL Domains	ART	ART Plus Chemotherapy	*P*
Global health status	54 (50 -67)	50 (33-50)	.005*
Functional scales			
Physical	92 (87-100)	87 (87-93)	.029
Role	67 (50-100)	33 (33-67)	.001*
Emotional	83 (50-92)	75 (50-83)	.671
Cognitive	83 (67-100)	100 (75-100)	.597
Social	83 (33-100)	50 (33-83)	.195
Symptom scales/items			
Fatigue	33 (11-56)	44 (11-67)	.343
Nausea/vomiting	0 (0-17)	0 (0-8)	.465
Pain	33 (17-67)	50 (33-100)	.017
Dyspnea	0 (0-33)	0 (0-33)	.195
Insomnia	33 (0-67)	0 (0-67)	.504
Appetite loss	33 (0-67)	0 (0-67)	.707
Constipation	0 (0-67)	0 (0-0)	.250
Diarrhea	0 (0-33)	0 (0-33)	.982
Financial problems	67 (33-100)	100 (67-100)	.018

NOTE. Data presented as median (interquartile range). Range of scores (0-100); 100 score is best for global health status and functional scales, and 0 score is best for symptom scales.
Abbreviations: ART, antiretroviral therapy; QOL, quality of life.
*Statistically significant at .01 level.

Fig 2. Changes in European Organization for Research and Treatment of Cancer quality-of-life questionnaire (EORTC-QLQ-C30) scores in the KAART (Kaposi Sarcoma AIDS Anti-Retroviral Therapy) study from baseline to month 12. Box and whisker plot of EORTC-QLQ-C30 scores; for each measurement, the first box and whisker (blue dot) represents baseline scores, and the second box and whisker (red dot) represents month 12. Range of scores (0 to 100); 100 score best for functional scales and 0 score best for symptom scales. Boxes represent interquartile range, central lines represent medians, and whiskers represent adjacent values. *P* values for test of change between baseline and month 12, *P* < .01 considered statistically significant.
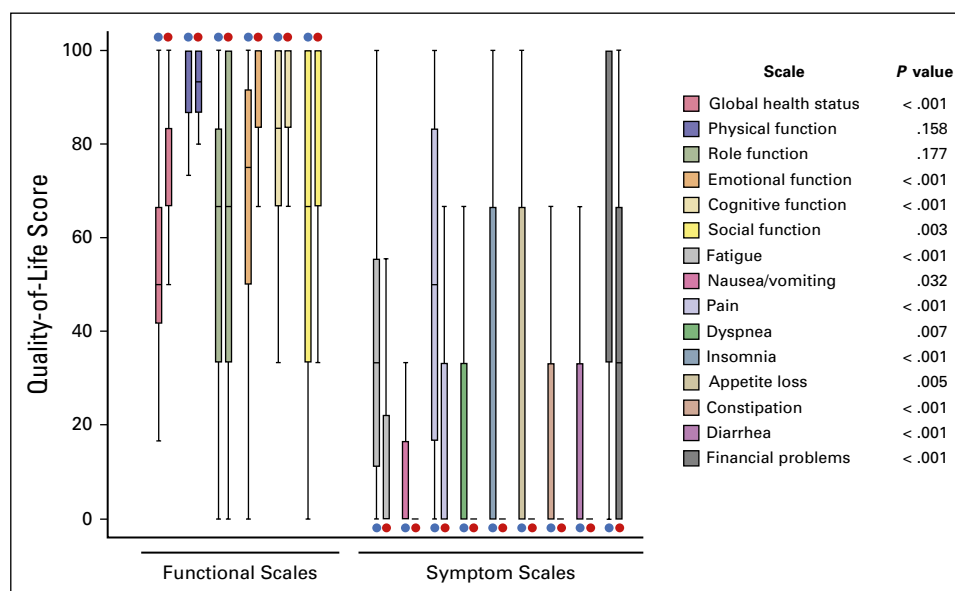
for GHS, emotional and cognitive functioning, fatigue, pain, and financial problems, as well as social functioning, insomnia, constipation, and diarrhea in the ART-alone arm. No statistically significant changes were seen between treatment arms. However, role functioning improved significantly in the chemotherapy arm but worsened in the ART-alone arm and strongly trended toward greater improvement in the chemotherapy arm (median change, 0 *v* +17; *P* = .011). Furthermore, GHS (median change, +13 *v* +17; *P* = .082) and pain (median change, −17 *v* −33; *P* = .1) showed possible trends toward increased improvement in the in the chemotherapy arm.

Table 2. Intra-arm and Inter-arm Comparative Changes in Quality-of-Life Scores Between Baseline and Month 12

QOL Domains	ART		ART and Chemotherapy		*P* (between arms)
	Median (IQR)	*P* (intra-arm)	Median (IQR)	*P* (intra-arm)	
Global health status	13 (0-17)	.007*	17 (0-50)	< .001*	.082
Functional scales					
Physical	0 (0-7)	.308	0 (−7 to 7)	.372	.929
Role	0 (−33 to 17)	.365	17 (0-67)	.006*	.011
Emotional	17 (0-33)	.001*	17 (0-33)	.001*	.884
Cognitive	17 (0-33)	.001*	17 (0-33)	.007*	.856
Social	0 (0-50)	.005*	0 (−17 to 50)	.174	.538
Symptom scales					
Fatigue	−22 (−56 to 0)	< .001*	−33 (−44 to −11)	< .001*	.430
Nausea/vomiting	0 (0-0)	.194	0 (0-0)	.067	.955
Pain	−17 (−50 to 0)	< .001*	−33 (−83 to 0)	.002*	.100
Dyspnea	0 (−33 to 0)	.011	0 (0-0)	.256	.200
Insomnia	−33 (−67 to 0)	< .001*	0 (−67 to 0)	.013	.417
Appetite loss	0 (−67 to 0)	.020	0 (−67 to 0)	.096	.536
Constipation	0 (−67 to 0)	.001*	0 (−33 to 0)	.030	.520
Diarrhea	0 (−33 to 0)	.006*	0 (−33 to 0)	.074	.738
Financial problems	−33 (−67 to 0)	.001*	−33 (−100 to 0)	.003*	.615

NOTE. Range of scores (0-100); 100 score best for global health status and functional scales and 0 score best for symptom scales
Abbreviations: ART, antiretroviral therapy; IQR, interquartile range; QOL, quality of life.
*Statistically significant at 0.01 level.

Relationship Between GHS, Role Function, and Pain With Clinical Parameters

In univariable analyses, $CD4^+$ count and HIV viral load showed no correlation with the GHS at baseline, month 6, and month 12, nor did the change in $CD4^+$ and viral load between baseline and month 12 correlate with the change in GHS. Likewise, adherence did not influence either GHS at month 12 or the change in GHS. The majority of participants reported good and excellent adherence. Adherence was analyzed in relation to temporal changes between baseline and month 12 in GHS, and no significant difference between GHS for each adherence category was noted.

Cumulative adverse events during the trial did not correlate with either the GHS at month 12 or the change in GHS between baseline and month 12. To assess whether the severity rather than the cumulative adverse events affected the GHS, the SAEs were analyzed (Data Supplement). There was a possible trend toward an association between greater cumulative SAEs and improved GHS at month 12 ($P = .08$), suggesting short-term chemotherapy-related adverse events may have been balanced by 12-month KS outcomes.

GHS was associated with KS regression. Indeed, those with a complete clinical response at month 12 reported the highest GHS, whereas those with progressive disease showed no improvement. There were statistically significant differences in GHS at month 12 between those with complete, partial, stable, and progressive clinical response ($P = .006$; Data Supplement).

Regardless of the treatment group, there was a significant worsening in role function in those who had stable or progressive KS ($P < .006$). There was a strong trend toward a significant improvement in pain in those who had a partial or complete response to the KS ($P < .011$).

Multivariable Analysis of Factors Associated With Global Health Score Over Time

In a multivariable analysis, time in the study showed a possible trend toward improved GHS, especially month 12 versus month 3, which had significantly higher $\log_{10}$ GHS scores ($P = .002$). Importantly, having a complete or partial response versus stable response or progression had a strong trend toward significance associated with increased GHS ($P = .011$). An intention-to-treat evaluation of treatment arm did not show significant differences between arms in GHS (Data Supplement). In summary, both treatment arms showed an increase in GHS over time, especially in month 12. Those who showed a response to treatment showed better improvement in GHS.

DISCUSSION

To our knowledge, KAART is the first study to document the effect of HIV-associated KS on QOL in the era of effective ART and the first to evaluate the influence of ART with or without chemotherapy on QOL parameters in this population. Baseline QOL scores highlight the effect of advanced KS, with global health scores, role, and social function particularly affected by KS. Pain represented the highest level of symptoms, which is consistent with the high tumor burden (T_1 disease) seen in 89% of patients.[13] It is important to contrast findings from this study to those from a study conducted in Zimbabwe demonstrating a deterioration in QOL despite chemotherapy or radiotherapy in HIV-associated KS before the availability of ART.[8]

In the KAART trial, symptomatic benefit to patients in the overall study was evidenced by improvement in most scales. Fatigue, pain, insomnia, constipation, and financial problems demonstrated the greatest improvement. Many symptomatic improvements may be explained by therapy with ART, which improves immunologic function.[19] For many of the patients, the hope that ART has given them, especially at a time when this was not available through the government sector, could have been responsible for a positive outlook associated with improved QOL. The improvement in financial problems suggests some may have been able to be employed. Also, patients who received therapy in this trial may have saved funds normally spent on visiting a variety of health care professionals and buying expensive supplements.

Improved role function may be the domain most affected by being assigned to the early chemotherapy arm. Patients randomly assigned to ART alone demonstrated no improvement at month 12, whereas the chemotherapy arm showed a statistically significant improvement. This was possibly due to the better clinical response in those receiving chemotherapy: a 27% absolute increase in overall response at month 12 (66%

v 39%).[13] The improvement in pain was associated with the response of the KS to therapy, although analgesia that some patients received may have provided added palliative benefit. At month 12, both arms had improvement in pain scales (decrease from 50 to 17 in the chemotherapy arm and from 33 to 17 in the ART arm), with comparable 12-month scores, reflecting residual pain. There was a borderline trend to greater improvement in pain scales in those who were randomly assigned to receive chemotherapy, and this could be due to the better clinical response, because those with a clinical response to the tumor trended to have improvement in pain, as described previously.[9]

Improvement in QOL was also associated with KS regression for several important domains. Improvements in GHS, the best indicator of overall QOL, as well as role function were significantly associated with responses at month 12, whereas there was a strong trend between 12-month response and decreased pain. Interestingly, those with increased severe adverse events in the study showed a better GHS at month 12. This could indicate an acceptable therapeutic index, whereby the beneficial effects of treatment outweighed chemotherapy-associated AEs. Overall, the KAART study demonstrated improvement in GHS QOL over time and especially at the completion of trial, irrespective of the treatment arm.

This study had some limitations. Crossover between arms limited our ability to fully measure the effect of chemotherapy in addition to ART on QOL measures. Some KS-specific factors associated with QOL, such as edema or satisfaction, were not fully captured using the EORTC QLQ-C30. QOL tools for HIV-infected individuals (Functional Assessment of HIV[12] and Medical Outcomes Study-HIV[11]) supplemented with KS modules (Kaposi's sarcoma module[8]) or questions could have provided additional disease-specific QOL data.

Despite these limitations, this study confirms an important morbidity benefit in a low-resource setting with ART and generic chemotherapy. Because people with HIV-associated KS are living substantially longer with the availability of ART, the quality of their lives will become increasingly important. The study demonstrates the value of quantification of QOL in patients with HIV-associated malignancies in low-resource settings, because it may be affected positively or negatively by cancer-specific therapies. Importantly, results show that ART is associated with improved 12-month QOL in this patient population and that no long-term deleterious effects of chemotherapy were observed in QOL measures. Early chemotherapy using agents that are available in resource-limited settings in patients with advanced disease leads to improved tumor regression, and our study supports tumor regression as an important treatment goal for HIV-associated KS, given the associated measurable improvements in GHS, role function, and pain.

Decreased morbidity is an important goal of KS management. Patients with advanced HIV-associated KS benefit from ART, regardless of the addition of chemotherapy. A greater satisfaction was observed with patient functioning, symptom, and financial relief. QOL improved in patients whose tumor regressed, and this supports a role for KS-specific therapies to decrease morbidity in patients with a high tumor burden (T_1 disease). QOL results from this study inform management of HIV-associated KS, and our findings are particularly important for cancer control programs in sub-Saharan Africa.

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