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https://escholarship.org/uc/item/45j1w6kx

Journal

Clinical Infectious Diseases, 67(2)

ISSN

1058-4838

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Publication Date

2018-07-02

DOI

10.1093/cid/ciy044

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Clinical Infectious Diseases

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As-Needed Vs Immediate Etoposide Chemotherapy in Combination With Antiretroviral Therapy for Mild-to-Moderate AIDS-Associated Kaposi Sarcoma in Resource-Limited Settings: A5264/AMC-067 Randomized Clinical Trial

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Background. Mild-to-moderate AIDS-associated Kaposi sarcoma (KS) often responds to antiretroviral therapy (ART) alone; the role of chemotherapy is unclear. We assessed the impact of immediate vs as-needed oral etoposide (ET) among human immunodeficiency virus (HIV)–infected individuals with mild-to-moderate KS initiating ART.

Methods. Chemotherapy-naive, HIV type 1–infected adults with mild-to-moderate KS initiating ART in Africa and South America were randomized to ART (tenofovir/emtricitabine/efavirenz) alone (chemotherapy "as-needed" arm) vs ART plus up to 8 cycles of oral ET (immediate arm). Participants with KS progression on ART alone received ET as part of the as-needed strategy. Primary outcome was ordinal as follows: failure, stable, and response at 48 weeks. Secondary outcomes included time to initial KS progression, KS-associated immune reconstitution inflammatory syndrome (KS-IRIS), and KS response.

Results. Of 190 randomized participants (as-needed = 94, immediate = 96), the majority were men (71%) and African (93%). Failure (53.8% vs 56.6%), stable (16.3% vs 10.8%), and response (30% vs 32.5%) did not differ between arms (as-needed vs immediate) among those with week 48 data potential (N = 163, $P = .91$). Time to KS progression ($P = .021$), KS-IRIS ($P = .003$), and KS response ($P = .003$) favored the immediate arm. Twenty-five participants died (13%). Mortality, adverse events, CD4+ T-cell changes, and HIV RNA suppression were similar at 48 weeks.

Conclusions. Among HIV-infected adults with mild-to-moderate KS, immediate ET provided early, nondurable clinical benefits. By 48 weeks, no clinical benefit was observed compared to use of ET as needed. Mortality was high and tumor response was low.

Clinical Trials Registration. NCT01352117.

Keywords. Kaposi sarcoma; HIV; etoposide; chemotherapy; antiretroviral therapy.

Kaposi sarcoma (KS) caused by KS-associated herpesvirus (KSHV) was among the earliest recognized manifestations of the AIDS epidemic [1]. Following introduction of antiretroviral therapy (ART), AIDS-KS incidence decreased [2–4], but incident cases occur despite successful ART [5]. In resource-limited settings where human immunodeficiency virus (HIV) and KSHV coinfection is common, KS remains a significant contributor to morbidity and mortality [6].

KS presents along a continuum from mild to advanced disease and may appear or worsen dramatically as a manifestation of immune reconstitution (Kaposi sarcoma–associated immune reconstitution inflammatory syndrome [KS-IRIS]). For all stages of AIDS-KS, ART is an essential treatment component. While advanced-stage KS is generally considered to also require chemotherapy [7], chemotherapy's role in mild-to-moderate KS is poorly defined. In North America and Europe, up to 60% of people with KS show lesion regression with ART alone [8, 9], whereas lower response rates have been observed in Africa. Factors associated with poorer outcomes include low CD4

Received 8 November 2017; editorial decision 8 January 2018; accepted 18 January 2018; published online January 22, 2018.

Presented in part: 9th International AIDS Society Conference on HIV Pathogenesis Treatment and Prevention. Paris, France, 23–26 July 2017. Abstract 710.

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Clinical Infectious Diseases® 2018;67(2):251–60

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DOI: 10.1093/cid/ciy044

count, high KSHV-DNA, low body mass index, anemia, and systemic signs and symptoms [10–14]. Given high mortality rates in resource-limited settings, better KS management strategies are needed to improve outcomes.

The World Health Organization (WHO) recommends immediate ART initiation for HIV-infected adults with KS but notes that "no randomized controlled trials or observational studies have been specifically designed or powered to address the value of adding chemotherapy to ART compared to ART alone, in patients with mild-to-moderate KS" [7]. Orally administered etoposide (ET) induces KS regression without excessive toxicity [15–17]. Although easily incorporated into outpatient treatment regimens, knowledge gaps exist concerning oral ET use in decentralized settings [7]. The randomized clinical trial A5264/AMC (AIDS Malignancy Consortium)-067 was designed to address these gaps. We hypothesized that response of mild-to-moderate KS to ART would be improved by immediate addition of oral ET compared to as-needed ET for disease progression.

METHODS

Study Population and Setting

Participants were HIV type 1 infected, aged ≥18 years with biopsy-confirmed mild-to-moderate KS, naive to chemotherapy and initiating or reinitiating ART. Prior ART experience was limited to 14 days after KS onset within the previous 6 months. Mild-to-moderate KS was defined as stage T0 (confined to skin and/or lymph nodes and/or minimal oral KS) and some presentations of stage T1 [18], which align with the WHO definition of mild-to-moderate KS [7]. Allowable stage T1 features included tumor-associated edema limited to area(s) of cutaneous KS without significant functional impairment; flat oral KS lesions confined to the soft palate, hard palate, gums, and buccal mucosa; and asymptomatic gastrointestinal lesions.

Additional inclusion criteria included 5 bidimensionally measurable cutaneous marker lesions or total marker lesion surface area ≥700 mm^2; absolute neutrophil count (ANC) ≥1000 cells/mm^3; hemoglobin ≥9.0 g/dL (≥7.5 g/dL if transfusion readily available); platelets ≥100 000/mm^3; creatinine clearance ≥60 mL/min; aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase <5 times the upper limit of normal (ULN); bilirubin ≤1.5 times ULN. Pregnant and breastfeeding women were excluded.

Study Design

A5264/AMC-067 was a randomized, open-label trial of ART with immediate initiation of low-dose oral ET (immediate arm) compared to ART with as-needed ET (as-needed arm). The study was conducted at 10 sites in 7 countries in sub-Saharan Africa and South America. Participants were randomized 1:1 using permuted blocks and institutional balancing [19] to the immediate and as-needed arms. Stratification included CD4 count ≥200 and <200 cells/mm^3 and ART treatment naive vs experienced. All participants received efavirenz/tenofovir-DF/emtricitabine 600 mg/300 mg/200 mg as a single coformulated tablet daily (Atripla, Merck) or tenofovir-DF/emtricitabine (Truvada, Gilead) plus efavirenz (Stocrin, Merck).

Etoposide (VePesid, Bristol-Myers Squibb) was given as a single 50-mg capsule on days 1–7 of each 14-day cycle. For participants without partial or complete tumor response after 2 cycles and no toxicity >grade 2, ET was escalated to 100 mg on days 1–7, every 14 days. A cycle could be delayed for ≤14 days for toxicity management. Up to 8 ET cycles were administered (2 cycles during dose titration, 6 at maximum dose). Participants who did not tolerate ET dose escalation received a maximum of 6 cycles. Participants assigned to the as-needed arm could receive ET after confirmation of KS progression by an independent endpoint review committee (IERC).

Participants received clinical and laboratory evaluation at screening, entry, and biweekly until week 16, and then at increasing intervals until week 96. Adherence assessments were conducted at weeks 2 and 4 and then every 4 weeks through week 24. Signs, symptoms, and laboratory results were graded according to Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (http://rsc.tech-res.com/safetyandpharmacovigilance/). ET doses were delayed, modified, and/or discontinued for graded adverse events; adverse events that recurred after dosage reduction or that lasted longer than 3 weeks required ET discontinuation.

Key Study Outcomes

The primary outcome was a composite endpoint, ordered from worst to best as follows: failure: progressive KS disease (PD) at week 48 compared to study entry, initiation of new KS treatment, or loss to follow-up (including death and missed visit) by week 48; stable: without PD, without partial response (PR), without complete response (CR) at week 48 compared to study entry and without initiation of a new KS treatment by week 48; and response: PR or CR at week 48 compared to study entry, without initiation of new KS treatment by week 48.

KS response at week 48 was categorized as CR, PR, stable, or PD compared to baseline, as previously described [18, 20], with additional refinements including quantification of tumor-associated edema.

Suspected KS-IRIS was defined as PD within 12 weeks of ART initiation associated with increased CD4+ cell count ≥50 cells/mm^3 and/or decreased plasma HIV RNA ≥0.5 $\log_{10}$ copies/mL below the entry value. Full eligibility criteria and outcome definitions are included in the study protocol (Supplementary Materials, www.actgnetwork.org).

Study Oversight and Conduct

The National Institutes of Allergy and Infectious Diseases (NIAID) funded the study through the AIDS Clinical Trials Group (ACTG), with additional funding from the National Cancer Institute through the AMC. An IERC of 8 KS experts

who were not members of the study team reviewed KS progressions, including suspected KS-IRIS. The NIAID Complications and Co-infections Data and Safety Monitoring Board monitored the study at least yearly. At the fifth review in March 2016, which included the third interim efficacy analysis, the board recommended closure for futility in the primary outcome analysis.

Sample Size and Statistical Methods

In the as-needed arm, we expected 30% PD, death, or initiation of KS treatment other than ET and 30% PR or CR [8, 9]. We projected a 10% reduction in PD and a 15% increase in PR or CR in the immediate arm. We further assumed a uniform loss of ≤10% of participants across study arms due to early discontinuation, death, or missed week 48 visits. The planned sample size of 234 per arm provided 90% power to conclude superiority of the immediate arm, in a rank-based test for ordered categorical outcomes with a 2-sided type I error of 5%. Haybittle-Peto stopping boundaries were specified for the interim efficacy analyses [21].

The primary endpoint analysis was restricted to participants who had week 48 data potential by the date when study closure was announced. The van Elteren test was used to compare study arms. Logistic regression analyses was performed to assess predictors of week 48 failure, defined as a binary variable using the failure category of the primary endpoint. For analysis of time to failure, Kaplan-Meier estimation and log-rank tests that used the first event that occurred in the composite endpoint were performed. For analyses of time to initial KS progression, KS-IRIS, and initial KS response, Gray's approach was used to compare cumulative incidence distributions between arms with initiation of alternate KS treatment and death modeled as competing risks [22]. Factors associated with time to initial KS progression were assessed using subdistribution hazards [23] and cause-specific hazards models. Results were similar in both, and only results from the cause-specific hazards models are presented. In addition to the screening CD4+ count, the most recently measured preceding CD4+ count was considered as a potential predictor. For variable selection, each predictor of interest was first considered in a separate simple model that only controlled for study arm, and $P < .20$ determined entry into a full model. Then, all-subsets variable selection approach was used with a $P \leq .05$ as a criterion to retain in the final, reduced model, while keeping the study arm throughout the procedure.

Wilcoxon rank sum tests were used to compare continuous measures between groups and Fisher exact tests were used for binary or categorical measures. Proportions are provided for binary or categorical variables with Clopper-Pearson confidence intervals (CIs) for binary variables. All tests were 2-sided at 5% significance, unless specified otherwise, and were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina).

Ethical Statement

Sites obtained approval from local ethics committees. Participants provided written informed consent.

RESULTS

From November 2011 through March 2016, 192 participants were enrolled; 190 were randomized to begin study interventions (94 as-needed, 96 immediate; Figure 1). Baseline characteristics were similar across arms (Table 1). The majority of participants were men (71%) and African (93%). Median age was 34 years (Q1,Q3:29,41). Median CD4 count was 184 cells/mm^3 (78 325); 18% had a CD4 count <50 cells/mm^3, with nonsignificant differences across arms (22% immediate, 15% as-needed). Only 1 participant was ART experienced. KS stage was T1 in 61%, presence of oral KS 58%, and edema 60%. KS was confined to the skin in 15% of participants, with a higher proportion in the immediate arm (20% vs 10%).

Of 190 randomized participants, 163 (86%; 80 as-needed, 83 immediate) were included in the primary analysis. Included participants were similar to the overall population with respect to age, sex, race, and CD4+ counts and were balanced across the arms (Table 1). The primary analysis group differed from the overall cohort in frequency of abnormal baseline screening chest X-ray (27% vs 7%) and by distribution of site countries (Supplementary Table 1).

There was no difference between arms in the composite and ordinal primary outcomes of failure, stable, or response (Table 2). Failure in the as-needed arm was primarily from KS progression and was primarily due to initiation of non-ET chemotherapy in the immediate arm (31 immediate, 12 as-needed). Death and loss to follow-up were similar in both arms. The primary outcome did not differ according to CD4+ cell stratum. Overall, 52 immediate participants achieved initial response without alternative chemotherapy (ART+ET) and 29 as-needed participants without ET initiation (ART only), and 27/52 (52%) immediate and 22/29 (76%) as-needed had responses at week 48.

In the sensitivity analysis that excluded receipt of alternative chemotherapy as failure, there was a higher KS response rate (45% vs 35%) and lower failure rate (39% vs 49%) in the immediate arm than in the as-needed arm (Table 2).

In simple models that evaluated the associations between treatment failure and baseline characteristics, more advanced KS (stage T1, higher cutaneous lesion count, presence of edema, and edema interfering with function) was associated with increased odds of failure (Table 3, simple models), as were lower Karnofsky performance status (KPS) and low albumin ($P < .05$). Female sex, cutaneous-only KS, and lower ANC were associated with decreased odds of treatment failure ($P < .05$). All-subsets variable selection led to the reduced multivariate model (Table 3, final model); female sex (odds ratio [OR], 0.45; 95% CI, 0.21,0.96) and lower ANC (OR, 0.36; 95% CI, 0.16,0.79) were associated with reduced odds of failure while low albumin

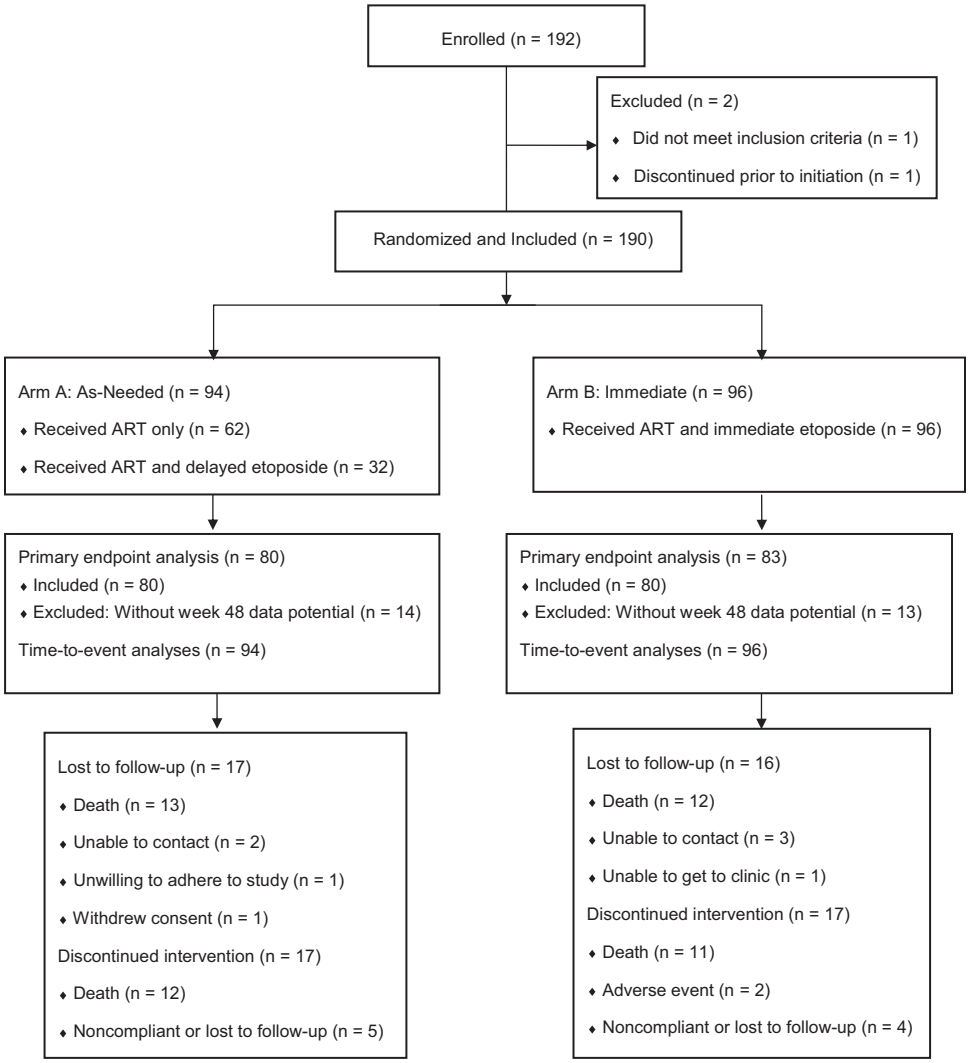

Figure 1. A5264 study Consort diagram. Abbreviation: ART, antiretroviral therapy.

(OR, 4.48; 95% CI, 2.09, 9.58) and KPS <90 (OR, 2.34; 95% CI, 1.12, 4.88) were associated with higher odds of failure.

Among all enrolled participants (N = 190), time to failure (composite primary endpoint) was more rapid in the as-needed arm than in the immediate arm (P = .080; Figure 2A). Median time to KS progression was faster in the as-needed arm than in the immediate arm (24.1 vs 96.6 weeks, P = .021; Figure 2B) and differed according to CD4+ count stratum (Supplementary Figure 1a and 1b). Factors associated with initial KS progression were similar to those associated with treatment failure, with some exceptions (Table 4). In simple models, low albumin and hemoglobin values, KPS <90, abnormal screening chest X-ray, stage T1, >50 cutaneous KS lesions, and edema interfering with function were associated with increased hazards for progression. Screening CD4+ count <200 cells/mm^3 was associated with decreased hazard for progression. Time-updated current CD4+ cell count was not statistically significant. In the final, reduced-model, as-needed arm, low albumin, KPS <90, and presence of raised lesions were associated with increased hazard for KS progression, while screening CD4 count <200 cells/mm^3 was associated with a decreased hazard.

Protocol-defined suspected KS-IRIS occurred in 21 participants (22%) in the as-needed arm and in 7 (7%) in the immediate arm. Time to KS-IRIS was more rapid among participants in the as-needed arm than in the immediate arm (P = .003; Figure 2C).

Time to initial KS response was more rapid in the immediate arm than in the as-needed arm (P = .003) (Figure 2D), with greater differences between the arms observed for the ≥200 cells/mm^3 CD4+ stratum (Supplementary Figures 2a and 2b).

Supporting high adherence, virologic suppression (HIV RNA <400 copies/mL) occurred in 97% of participants by week 48 and was similar between arms (95% in the as-needed arm, 99% in the immediate arm; P = .56). At week 48, in the as-needed arm, the median CD4 count was 348

Table 1. Characteristics of Study Participants at Screening or Baseline (Study Entry) According to Randomized Treatment

Characteristic	As-Needed Arm[a]	Immediate Arm[b]	*P* Value
Number	94	96	N/A
Female	28 (30%)	27 (28%)	.873
Age[c]	34 (28, 41)	35 (30, 41)	.693
Self-identified racial group			
Black or African	89 (95%)	88 (92%)	.649
Asian	0	1	…
White	2	5	…
Other	3	2	
Hispanic or Latino	8 (9%)	8 (8%)	.934
Country	…	…	.993
Brazil	4 (4.3%)	5 (5.2%)	…
Kenya	15 (16.0%)	13 (13.5%)	…
Malawi	30 (31.9%)	32 (33.3%)	…
Peru	2 (2.1%)	3 (3.1%)	…
South Africa	6 (6.4%)	6 (6.3%)	…
Uganda	28 (29.8%)	30 (31.3%)	…
Zimbabwe	9 (9.6%)	7 (7.3%)	…
Weight (kg)[c]	60.6 (53.9, 67.4)	62.0 (55.0, 70.8)	.307
Body mass index (kg/m^2)[c,d]	21.9 (19.9, 23.6)	22.0 (19.7, 24.8)	.680
Prior antiretroviral exposure	0 (0%)	1 (1%)	N/A
Hemoglobin (g/dL)[c]	12.0 (10.7, 13.3)	11.9 (10.4, 13.3)	.845
Neutrophils (per mm^3)[c]	1698 (1280, 2790)	2067 (1410, 2765)	.260
Albumin (g/dL)[c]	3.7 (3.1, 4.0)	3.6 (3.2, 4.0)	1.00
Screening CD4+ cell count (per mm^3)[c]	190 (88, 325)	165 (63, 327)	.384
Plasma human immunodeficiency virus RNA ($\log_{10}$ copies/mL)[c]	5.1 (4.5, 5.5)	5.1 (4.6, 55)	.911
Positive hepatitis B surface antigen[d]	7 (8%)	9 (9%)	.796
KS stage T0[e]	35 (37%)	40 (42%)	.556
Oral KS present	55 (59%)	55 (57%)	1.000
Edema present	57 (61%)	54 (56%)	.559
Greater than 50 cutaneous KS lesions	43 (46%)	44 (46%)	.963
Karnofsky score ≥90	59 (63%)	65 (68%)	.429
Screening X-ray abnormal[d]	19 (21%)	27 (28%)	.241

Baseline results are presented, unless noted as screening.

Abbreviations: KS, Kaposi sarcoma; N/A, not applicable.

[a]As-needed arm: antiretroviral therapy alone or with delayed etoposide.

[b]Immediate arm: antiretroviral therapy with immediate etoposide.

[c]Median with first and third quartiles (Q1, Q3).

[d]The following had missing results: body mass index (1 missing), hepatitis B surface antigen (3 missing), and screening X-ray (2 missing).

[e] AIDS Clinical Trials Group criteria.

cells/mm^3 (Q1,Q3: 186,469) and median change was 125 cells/mm^3 (39,196). In the immediate arm, the median was 338 cells/mm^3 (214,458) and median change was 120 cells/mm^3 (62,208).

Twenty-five participants died (13 as-needed, 12 immediate). No deaths were considered related to study treatment. CD4 + cell count <50 cells/mm^3, low albumin, and grade ≥1 hemoglobin were associated with mortality in univariate analyses ($P < .05$). Mortality was higher in participants with stage T1 than in those with stage T0, but this difference was not statistically significant (16% vs 9%, $P = .27$). There were 89 participants with grade 3 or 4 adverse events, 47 in the as-needed arm (50%) and 42 in the immediate arm (44%; Supplementary Table 3). Of 65 grade 3 or 4 laboratory events overall, 47 were hematological events, primarily (37/47) neutropenia, evenly divided by arms. Hepatic and renal adverse events were infrequent. A total of 240 new diagnoses, primarily infections, were reported in 98 participants and evenly distributed by arm.

DISCUSSION

In this randomized trial in which we compared immediate vs as-needed oral ET in individuals with mild-to-moderate AIDS-KS initiating ART, we found no strong evidence to support the superiority of immediate ET based on the primary endpoint. We detected some benefits of immediate ET, including delayed KS progression, decreased suspected KS-IRIS events, and decreased time to initial KS response. Together, these findings suggest that immediate ET with ART had biological effects

Table 2. Primary Efficacy Outcome and Sensitivity Analyses

Outcome	Outcome Components	As-Needed (N = 80)	Immediate (N = 83)	*P* Value[a]
Primary endpoint	E1 (failure)[b]	43 (53.8%)	47 (56.6%)	.911
	Progression	21	7	…
	Initiation of alternate Kaposi sarcoma treatment	12	31	…
	Death	10	8	…
	Lost to follow-up	3	3	…
	E2 (stable)	13 (16.3%)	9 (10.8%)	…
	E3 (response)	24 (30.0%)	27 (32.5%)	
	Partial response	21	23	…
	Complete response	3	4	…
Sensitivity analysis[c]	E1 (failure)	39 (48.8%)	32 (38.6%)	.170
	Progression	26	21	…
	Death	10	8	…
	Lost to follow-up	3	3	…
	E2 (stable)	13 (16.3%)	14 (16.9%)	…
	E3 (response)	28 (35.0%)	37 (44.6%)	…
	Partial response	25	31	…
	Complete response	3	6	…

[a]van Elteren test with CD4 stratification.

[b]Two participants in as-needed and 2 participants in immediate arm died after initiating alternate Kaposi sarcoma (KS) treatment. One participant in as-needed arm was lost to follow-up after initiating alternate KS treatment.

[c]Sensitivity analysis that does not include initiation of alternate KS treatment as the worst outcome.

Table 3. Associations With Failure in Week 48 Primary Endpoint

		Simple Model[a]	Full Model[b]	Final Model[c]	
Variable	Covariate[d]	OR (95% CI)	OR (95% CI)	OR (95% CI)	*P* Value
Study arm	As-needed vs immediate	NA	0.91 (0.45, 1.87)	0.95 (0.47, 1.90)	.879
Age (years)	≥35 vs <35	0.92 (0.50, 1.71)	…	…	…
Sex	Female vs male	0.49 (0.25, 0.97)*	0.48 (0.21, 1.09)	0.45 (0.21, 0.96)	.039
Scr: CD4 cell count, stratification factor	<200 vs ≥200 (cells/mm^3)	0.75 (0.40, 1.39)	…	…	…
Scr: CD4 cell count	<50 vs ≥50 (cells/mm^3)	0.89 (0.41, 1.94)	…	…	…
W0: Human immunodeficiency virus RNA	≥5.0 vs <5.0 ($\log_{10}$ copies/mL)	0.87 (0.47, 1.63)	…	…	…
W0: Albumin grade	Grade ≥1 vs normal	4.40 (2.16, 9.00)*	3.98 (1.47, 10.81)	4.48 (2.09, 9.58)	<.001
W0: Absolute neutrophil count grade	Grade ≥1 vs normal	0.37 (0.18, 0.76)*	0.39 (0.17, 0.89)	0.36 (0.16, 0.79)	.011
W0: Hemoglobin grade	Grade ≥1 vs normal	2.16 (0.89, 5.28)	1.23 (0.34, 4.46)	…	…
Scr: Karnofsky score	<90 vs ≥90	2.24 (1.15, 4.34)*	1.92 (0.88, 4.18)	2.34 (1.12, 4.88)	.024
Scr: X-ray result	Abnormal vs normal	1.23 (0.61, 2.49)	…	…	…
W0: KS stage	T1 vs T0	2.18 (1.14, 4.15)*	0.63 (0.06, 7.06)	…	…
W0: Total cutaneous lesion count	>50 vs ≤50	2.00 (1.07, 3.76)*	1.03 (0.45, 2.35)	…	…
W0: Raised cutaneous lesions present	Yes vs no	1.53 (0.78, 3.03)	…	…	…
W0: Oral KS present	Yes vs no	1.67 (0.89, 3.14)	1.03 (0.38, 2.81)	…	…
W0: Oral KS minimal	Beyond minimal vs minimal or no oral KS	2.56 (0.66, 9.86)	2.63 (0.27, 25.50)	…	…
W0: Edema present	Yes vs no	2.34 (1.23, 4.44)*	2.68 (0.25, 28.19)	…	…
W0: Edema interferes with function	Yes vs does not interfere or no edema	4.06 (0.84, 19.48)	1.97 (0.32, 12.24)	…	…
W0: Cutaneous KS only	Yes vs no	0.38 (0.15, 0.93)*	1.31 (0.29, 5.94)	…	…

Abbreviations: CI, confidence interval; KS, Kaposi sarcoma; NA, not applicable; OR, odds ratio; Scr, screening; W0, baseline (study entry).

[a]Estimates are from simple logistic regression models, conducted separately for each covariate and including study arm only.

[b]Estimates are from a full model that included the study arm and all covariates that had *P* values < .20 in the simple models.

[c]Estimates are from a final, reduced model that included the study arm and all covariates that remained statistically significant ($P < .05$).

[d]The latter group is the reference group.

* $P < .05$.

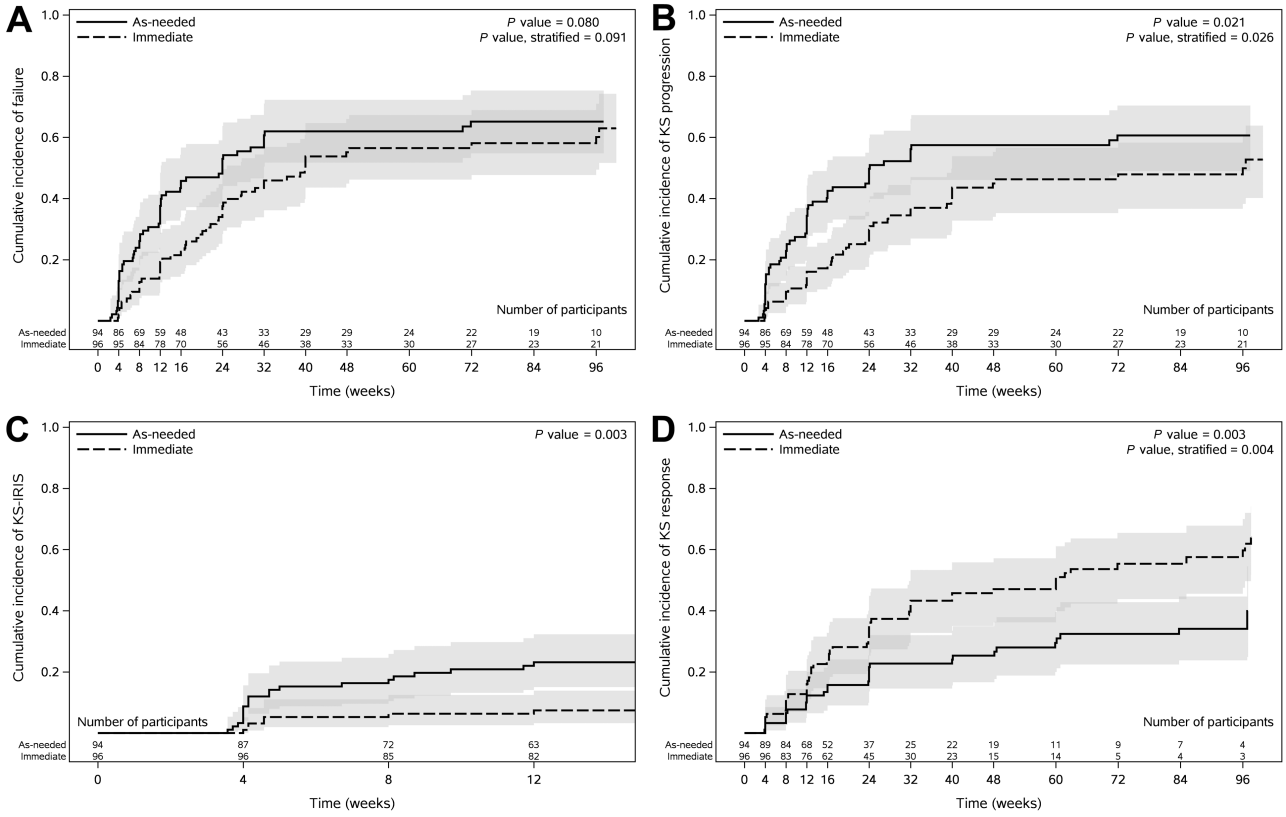

Figure 2. Kaplan-Meier plots with 95% confidence limits on (A) time to Failure, (B) time to initial KS progression, (C) time to suspected KS-IRIS, (D) time to initial KS response. In (A), Failure is defined as KS progression, death or initiation of alternate KS treatment, and Failure time is the time of the earliest of these events. P-values are from log-rank test and log-rank test stratified by the screening CD4 count. In (B) and (D), p-values are from Gray's test and Gray's test stratified by the screening CD4 count, with death and initiation of alternate KS treatment as competing risks. In (D), delayed ET initiation in as-needed was also modeled as competing risk and reflects response on ART alone. In (C), the p-value is from Gray's test, and the time of suspected KS-IRIS is the time of initial KS progression meeting additional criteria for KS-IRIS. Abbreviations: KS, Kaposi sarcoma; KS-IRIS, KS–associated immune reconstitution inflammatory syndrome.

and provided short-term benefits but did not provide longer-term benefits as measured by the outcomes that defined our primary endpoint.

Our primary outcome was a composite of events that are highly relevant to AIDS-KS outcomes in low-resource settings, including death, loss to follow-up, initiation of chemotherapy other than ET (ie, intravenous chemotherapy), and KS progression compared to baseline at week 48. In interpreting a composite endpoint, understanding how each component contributes is critical. Mortality and loss to follow-up were similar across the arms, but alternative chemotherapy and KS progression differed.

Mortality was higher than in other HIV-infected treatment cohorts but comparable to that observed in other studies of AIDS-KS in resource-limited settings [24–26]. Most mortality occurred in the first 24 weeks, as observed in general ART cohorts worldwide [6, 27]. Many KS studies have found higher mortality in stage T1 than stage T0 [13, 14, 28]. In our study, the lack of a statistically significant difference in mortality between stage T1 and stage T0 KS may be explained by the restricted enrollment of only T1 presentations with asymptomatic oral KS or edema.

Alternative chemotherapy use was higher in the immediate arm. More frequent alternative chemotherapy in the immediate arm could have been a consequence of receiving ET immediately in a fixed 48-week period. In this scenario, we would expect the as-needed arm to catch up after 48 weeks. However, in both arms, nearly all PD and alternative chemotherapy use occurred by week 48. Progression rates were comparable to those in other studies among individuals with mild-to-moderate KS in resource-limited settings [29], but KS progression was higher in the as-needed arm.

Low albumin and KPS <90 were factors for increased risk of treatment failure and KS progression. KPS has long been used for prognostic purposes [30], so its association with adverse outcomes is not surprising. Likewise, low albumin is a measure of macronutrient deficiency or decreased hepatic function and has been associated with mortality in advanced HIV [31]. These measures of general health were more associated with treatment failure than KS stage or lesion characteristics.

KS-IRIS, a subset of KS progression, was suspected in 22% of those in the as-needed arm. In a multicenter cohort study,

Table 4. Associations With Time to Initial Kaposi Sarcoma Progression

Variable	Covariate[d]	Simple Model[a] HR (95% CI)	Full Model[b] HR (95% CI)	Final Model[c] HR (95% CI)	*P* Value
Study arm	As needed vs immediate	NA	1.82 (1.17, 2.83)	1.59 (1.05, 2.39)	.027
Age	≥35 vs <35 (years)	0.87 (0.58, 1.30)	…	…	…
Sex	Female vs male	0.66 (0.41, 1.05)	0.66 (0.40, 1.10)	…	…
Scr: CD4 cell count, stratification factor	<200 vs ≥200 (cells/mm^3)	0.61 (0.41, 0.92)*	0.59 (0.38, 0.94)	0.53 (0.35, 0.80)	.003
Scr: CD4 cell count	<50 vs ≥50 (cells/mm^3)	1.04 (0.61, 1.79)	…	…	…
Dichotomized time-updated CD4 cell count	<200 vs ≥200 (cells/mm^3)	1.22 (0.80, 1.85)	…	…	…
Time-updated CD4 cell count	Per 100 cells/mm^3	1.03 (0.94, 1.14)	…	…	…
W0: Human immunodeficiency virus RNA	≥5.0 vs <5.0 ($\log_{10}$ copies/mL)	1.06 (0.71, 1.59)	…	…	…
W0: Albumin grade	Grade ≥1 vs normal	2.31 (1.53, 3.47)*	2.35 (1.35, 4.11)	2.57 (1.70, 3.90)	<.001
W0: Absolute neutrophil count grade	Grade ≥1 vs normal	0.70 (0.43, 1.13)	0.72 (0.43, 1.22)	…	…
W0: Hemoglobin grade	Grade ≥1 vs normal	1.69 (1.03, 2.78)*	1.22 (0.65, 2.30)	…	…
Scr: Karnofsky score	<90 vs ≥90	1.52 (1.01, 2.29)*	1.45 (0.89, 2.38)	1.86 (1.22, 2.84)	.004
Scr: X-ray result	Abnormal vs normal	1.55 (1.01, 2.40)*	1.31 (0.81, 2.14)	…	…
W0: KS stage	T1 vs T0	1.70 (1.10, 2.63)*	1.57 (0.61, 4.06)	…	…
W0: Total cutaneous lesion count	>50 vs ≤50	1.61 (1.08, 2.42)*	0.93 (0.57, 1.53)	…	…
W0: Raised cutaneous lesions present	Yes vs no	1.39 (0.87, 2.21)	1.31 (0.79, 2.19)	1.64 (1.02, 2.65)	.041
W0: Oral KS present	Yes vs no	1.20 (0.79, 1.81)	…	…	…
W0: Oral KS minimal	Beyond minimal vs minimal or no oral KS	1.42 (0.69, 2.95)	…	…	…
W0: Edema present	Yes vs no	1.61 (1.05, 2.47)*	0.99 (0.40, 2.44)	…	…
W0: Edema interferes with function	Yes vs does not interfere or no edema	2.53 (1.31, 4.89)*	1.22 (0.56, 2.64)	…	…
W0: Cutaneous KS only	Yes vs no	0.57 (0.29, 1.11)	1.31 (0.56, 3.04)	…	…

Abbreviations: CI, confidence interval; HR, hazard ratio; KS, Kaposi sarcoma; NA, not applicable; Scr, screening; W0, baseline (study entry).

[a] Estimates are from simple Cox regression models, conducted separately for each covariate and including study arm only.

[b] Estimates are from a full model that included the study arm and all covariates that had *P* values < .20 in the simple models.

[c] Estimates are from a final, reduced model that included the study arm and all covariates that remained statistically significant (*P* < .05).

[d] The latter group is the reference group.

* *P* < .05.

administration of ART alone was associated with a nearly 3-fold increased hazard for development of KS-IRIS compared to ART combined with chemotherapy, and higher rates of KS-IRIS were observed in Africa compared to the United Kingdom [32, 33]. Our definition of suspected KS-IRIS concurs with that from a previous study [34], but the PD component of the definition cannot reliably distinguish between PD, which reflects the natural history of KS vs KS-IRIS, an event that, by definition, is mediated by immune reconstitution.

The strengths of this study include randomized design, diverse population from resource-poor areas where KS is common, strict definitions of KS progression and KS-IRIS, and independent review of all progression events. Our low loss to follow-up rate limited bias from unknown outcomes. Due to premature closure, the study was underpowered for full evaluation of some secondary objectives. KS extent was evaluated according to locally available diagnostic methods and did not require invasive techniques or scans to exclude visceral KS. Thus, advanced, visceral KS may have been missed or misdiagnosed during screening. Assessment of time-updated CD4+ counts in the analysis of time to KS progression was limited by the lack of CD4+ count data prior to week 12 and a high number of KS progressions prior to week 12 (about 52%), which may explain the unexpected direction of the association between screening CD4+ count and KS progression.

Ultimately, any decision about adjunctive use of chemotherapy for limited-stage KS requires an understanding of its potential risks and benefits. ET did not add short-term toxicity to ART, nor did it adversely affect CD4 count recovery or HIV suppression. As with previous studies of ET for KS [15, 17], neutropenia was the most common adverse event. Although immediate ET shortened time to KS response, prevented early progression, and inhibited suspected KS-IRIS, we found no effect on mortality. An interim review of another ongoing randomized trial also found that oral ET was inferior to a standard paclitaxel regimen in treating advanced, symptomatic KS [35]. Given the potential long-term risk of secondary leukemias and myelodysplasia with ET [36], the transient benefits do not justify ET's routine use for AIDS-KS treatment.

Our findings highlight the need for continued research into interventions capable of improving the suboptimal outcomes of individuals with mild-to-moderate KS. Until such interventions

are found, clinicians in resource-limited settings should recognize the lack of evidence supporting immediate adjunctive treatments for mild-to-moderate KS beyond ART alone.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. The site pathologists' biopsy-associated Kaposi Sarcoma diagnoses were confirmed by independent pathologists at Weill Cornell Medical College, Department of Pathology and Laboratory Medicine, New York. Site pathologists also participated in an Division of AIDS (DAIDS)-sponsored external quality assurance program. Oversight of this program was provided by the AIDS Clinical Trials Group Pathology External Review Committee (UM1-AI-06701). Pharmaceutical support was provided by Gilead, Merck, and Bristol-Myers Squibb pharmaceutical companies. We also recognize the support of Tim Wilkin for his support of the study in his capacity as chair of the AIDS Clinical Trials Group Committee on Opportunistic Infections and Malignancies.

Disclaimer. This article was written by C. G. in her capacity as an National Institutes of Health (NIH) employee, and the views expressed in this article do not necessarily represent those of the NIH. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute, National Institute of Allergy and Infectious Diseases, or the NIH.

Financial support. Research reported in this article was supported by the National Institute of Allergy and Infectious Diseases of the NIH (UM1 AI068634, UM1 AI068636, and UM1 AI106701) and by the National Cancer Institute (UM1CA121947). Further support was provided to M. H., A. M., and D. P. D. (CA190152) and to D. P. D. (CA019014).

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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