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A randomized controlled trial of HAART versus HAART and chemotherapy in therapy-naïve patients with HIV-associated Kaposi sarcoma in South Africa

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Abstract

Background—The optimal approach to HIV-associated KS (HIV-KS) in sub-Saharan Africa is unknown. With large-scale rollout of highly active antiretroviral therapy (HAART) in South Africa, we hypothesized survival in HIV-KS would improve and administration of chemotherapy in addition to HAART would be feasible and improve KS-specific outcomes.

Methods—We conducted a randomized, controlled, open-label trial with intention-to-treat analysis. Treatment-naïve patients from King Edward VIII Hospital, Durban, South Africa, a public-sector tertiary referral center, with HIV-KS, but no symptomatic visceral disease or fungating lesions requiring urgent chemotherapy, were randomized to HAART alone or HAART and chemotherapy (CXT). HAART arm received stavudine, lamivudine and nevirapine (Triomune®); CXT arm received Triomune® plus bleomycin, doxorubicin, and vincristine (ABV) every 3 weeks. When ABV was not available, oral etoposide (50-100 mg days 1-21 of a 28 day cycle) was substituted. Primary outcome was overall KS response using AIDS Clinical Trial Group criteria 12 months after HAART initiation. Secondary comparisons included: time to response, progression-free survival, overall survival, adverse events, HIV control, CD4 reconstitution, adherence and quality-of-life.

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Results—59 subjects were randomized to HAART, 53 to CXT. 12-month overall KS response was 39% in the HAART arm and 66% in the CXT arm (difference 27%; 95% CI 9%-43%, p=0.005). At 12 months, 77% were alive (no survival difference between arms, p=0.49), 82% had HIV viral load <50 copies/mL without difference between arms, (p=0.47); CD4 counts and QOL measures improved in all patients.

Conclusions—HAART with chemotherapy produced higher overall KS response over 12 months, while HAART alone provided similar improvement in survival and select measures of morbidity. In Africa, with high prevalence of HIV and HHV-8 and limited resources, HAART alone provides important benefit in patients with HIV-KS.

Keywords

Kaposi sarcoma; acquired immunodeficiency syndrome; human immunodeficiency virus; highly active antiretroviral therapy; South Africa

Introduction

Kaposi sarcoma (KS) is one of the commonest acquired immunodeficiency syndrome (AIDS)-defining malignancies. KS incidence decreased in the West with availability of highly active antiretroviral therapy (HAART),[1] but has increased in sub-Saharan Africa[2] due to high rates of human immunodeficiency virus-1 (HIV) and human herpesvirus-8 (HHV-8) co-infection, overburdening already frail health care systems. HIV-associated KS (HIV-KS) can cause substantial morbidity and mortality, which may be improved by chemotherapy. Most studies of chemotherapy for HIV-KS have been evaluated in the United States and Europe.[3-8] Pegylated liposomal doxorubicin and paclitaxel, have response rates ranging from 46-76% in the HAART era, but are not considered World Health Organization (WHO) essential drugs,[9] and are unavailable in many resource-poor settings.[3] In industrialized countries, HAART is usually combined with chemotherapy for advanced HIV-KS. However, prospective evaluation of HAART alone for treatment of HIV-KS has been limited,[7] and its efficacy in advanced HIV-KS is unknown.

Prior to availability of HAART in sub-Saharan Africa, HIV-KS mortality was high. In a prospective study in Zimbabwe in the 1990's comparing palliative chemotherapy, radiation or supportive care in 470 HIV-KS patients in the absence of available HAART, 12-month overall survival (OS) was only 30-40%.[10] Similar outcomes were seen in KwaZulu-Natal (KZN), South Africa.[11] In countries where HAART became widely available in 1996, OS of HIV-KS patients dramatically improved,[12] and HAART has become essential in HIV-KS management. With availability of HAART in the public sector of South Africa in 2003, we sought to more fully define the outcomes achieved with HAART in African patients with this common AIDS-defining malignancy, including those with advanced disease. Additionally, we hypothesized that chemotherapy started soon after initiation of HAART may further improve KS-specific outcomes with manageable toxicities.

Methods

Participants and Study Design

The Kaposi sarcoma AIDS Anti-Retroviral Therapy (KAART) Trial is a prospective, single-center, randomized, open-labelled trial comparing HAART to HAART combined with early chemotherapy (CXT) for HIV-KS. Treatment-naïve patients (no prior KS or HIV therapy) were recruited and enrolled from Dermatology Clinic at King Edward VIII Hospital, Durban, a public sector tertiary referral center for approximately 10.3 million people in KZN, South Africa. Enrolled patients had proven HIV and histologically confirmed KS.

Exclusion criteria included: KS requiring urgent chemotherapy (i.e. symptomatic visceral disease or fungating lesions), peripheral neuropathy, clinical congestive heart disease or ejection fraction < 50%, neutrophil count of <1,000u/L, hemoglobin < 9.0gm/dl, platelet count of $<75 \times 10^9$/L, serum creatinine >114.4 μmol/L, direct serum bilirubin >85 μmol/L, AST or ALT >2.5 times the normal range, and intensive phase of tuberculosis therapy. Patients were staged according to modified AIDS Clinical Trials Group (ACTG) criteria into "Good" and "Poor" risk groups, then randomized to HAART or CXT by 4-digit computer generated code. "Poor" risk subjects had any tumor, immune or symptom (TIS) ACTG staging feature associated with poor survival in HIV-KS. These included high-risk tumor features (T_1) (visceral disease, tumor-associated edema, or ulceration), advanced immune suppression (I_1) (CD4 less than 150 cells/μL); or systemic features of AIDS (S_1) (history of opportunistic infections, wasting, fevers, night sweats, poor performance status) (See Table, Supplemental Digital Content 1, ACTG Staging of KS).[13,14]

The study was done in accordance with principles of the Declaration of Helsinki and in compliance with Good Clinical Practice guidelines, with ethical approval from the Nelson R. Mandela School of Medicine institutional review board. All subjects provided written informed consent. This protocol was registered at clinicaltrials.gov (NCT00380770).

Treatment

HAART was fixed-dose combination stavudine (40 mg), lamivudine (150 mg) and nevirapine 200 mg (Triomune® Cipla-Medpro, Capetown, South Africa). This regimen was determined by availability to investigators through a donation from CIPLA during a period when antiretrovirals were unavailable in the public sector in South Africa, and was the first available public sector HAART regimen in KZN. Patients who developed resistance or drug toxicity received a second-line HAART regimen. Chemotherapy consisted of doxorubicin (20 mg/m^2 intravenously), bleomycin (10 U/m^2 intravenously) and vincristine (1.4 mg/m^2 intravenously, capped at 2 mg) (ABV)[15] every 3 weeks, started within the first month of initiation of HAART, with the goal of continuing chemotherapy for 2 cycles beyond maximal response. This relatively low cost regimen consists of agents on the WHO essential drug list.[9] Patients randomized to CXT were referred to public sector Oncology Clinic for chemotherapy administration. Patients in the HAART arm with inadequate KS response by month six or progressive KS requiring chemotherapy before month six were considered "HAART Treatment Failures", and offered chemotherapy based on both clinician judgement and evaluation of KS response using ACTG response criteria. Although planned protocol chemotherapy was ABV, oral etoposide (50-100 mg days 1- 21 of a 28 day cycle)[16] was used as alternative therapy in event of difficulties with chemotherapy drug supply or intravenous administration during the protocol. Dose modifications of HAART or chemotherapy were performed for toxicity or changes in renal function. Etoposide was started at 50 mg daily, but could be escalated to 100 mg in patients in subsequent cycles with inadequate KS tumor regression and no limiting toxicities.

Monitoring and Response Evaluation

At baseline, KS was evaluated by physical exam, chest radiograph and upper endoscopy. If indicated, bronchoscopy was performed. Endoscopy and chest radiography were repeated at six months in those with baseline visceral KS. Investigators in the Dermatology Clinic assessed clinical response every three months through month 12. Response evaluations included lesion counts, measurement of the sum product of the diameters (SPD) of 5 marker lesions, and assessment of nodularity. KS responses were graded as complete, partial, stable disease and progressive disease using previously described ACTG criteria (see Table, Supplemental Digital Content 2, ACTG KS Response Criteria).[13,14] Partial response (PR) required at least 50% decrease in number of lesions and/or SPD of marker lesions and/or

nodularity of lesions and no new lesions, while complete response (CR) required clinical resolution of all lesions and tumor-associated phenomenon. CR and PR were combined to determine overall response rate (ORR).

Monitoring included history and physical, complete blood count, serum chemistry, CD4 count and HIV-1 viral load (HIV-VL) performed at baseline, week two, week four and then monthly for 12 months. HIV-VL was measured by RNA PCR (HIV-1 QT kit: Roche Diagnostics, Rotkreuz, Switzerland) and CD4 counts were performed by Epics®XL Flow Cytometer and tetraOne® System (Beckman Coulter, Brea, CA). Toxicities were graded using Division of AIDS (DAIDS) toxicity scale. Adherence was assessed by a seven-day recall questionnaire,[17, 18] at week two, week four, and then monthly.

Previously validated QOL questionnaires (EORTC QOL-30),[19, 20] available in English and isiZulu, were completed at baseline and three-monthly. The questionnaire measures six functioning scales: physical, role, cognitive, emotional, social, and global QOL; and nine symptom scales and/or items: fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea and financial impact.[20] Differences greater than 10 points in QOL scores were considered to be clinically important.[21]

Primary and Secondary Outcomes

Primary outcome was comparison between arms of the proportion of patients with a KS PR or better at month 12 compared to baseline. Secondary outcomes included comparisons between arms of progression-free survival (PFS; time from randomization to progressive disease or death), time to response (TTR; time from randomization to achievement of PR or better), OS, adverse events, including the immune reconstitution inflammatory syndrome (IRIS), immunological and virologic parameters, adherence, QOL, and evaluation of modified ACTG prognostic criteria.

Statistical Analysis

Detection of 30% absolute improvement in ORR from 0.3 to 0.6 at month 12 with addition of chemotherapy (two-sided α=0.05, β=0.8) required 49 patients per arm. Assuming modest loss to follow-up, accrual goal was 120. Comparisons were based on intention-to-treat (ITT) analysis. Between arms, 12-month ORR, incidence of per-patient specific serious adverse events, and proportion of patients with undetectable HIV at month 12 were compared using Fisher's exact test. TTR was compared between arms using the Mantel-Haenszel rate ratio. PFS and OS were evaluated using Kaplan-Meier methodology with log-rank test to compare arms. Multivariate analysis of ACTG TIS risk factors employed Cox regression. Difference in CD4 reconstitution between arms was evaluated with the Mann-Whitney test. We evaluated intra-group changes in QOL scores between baseline and month 12 (Wilcoxon signed-rank test), changes between baseline and month 12 QOL scores between the two groups (Mann-Whitney test), and relationship between clinical responses and global QOL (Kruskal-Wallis test). Given multiple comparisons in QOL analysis, $p < 0.01$ was considered statistically significant, while $0.01 < p < 0.05$ represented important trends. In addition to ITT analyses, secondary planned as treated analysis was performed for 12-month ORR and OS.

Role of the Funding Sources

Study planning, design, implementation, analysis and write-up were performed entirely by the investigators. Funders had no role in conceptualization, planning, design, analysis or writing of this manuscript.

Results

Study Subjects, Randomization and Follow-up Events

From 2003-2009, 310 patients were screened; 112 were eligible, consented, and randomized, 59 to HAART and 53 to CXT, and followed for up to 12 months (Fig. 1). Table 1 illustrates baseline demographic characteristics. Notably, 110 of 112 were black, 55% were women, 69% were from the urban area of Durban, and 31% were rural residents of KZN. 93% were poor-risk based on modified ACTG criteria: 89% had advanced disease with a high tumor burden (T_1), 54% had a CD4 count <150 cells/μL (I_1) (58% had CD4 <200 cells/μL) and 42% had inflammatory "B" symptoms or a history of opportunistic infection (S_1), including a history of treated tuberculosis in 16 subjects.

Of patients assigned to HAART, 13 (22%) were "HAART treatment failures" and received chemotherapy, 10 between months two and six, and three after month six. Of patients randomized to CXT 15 (28%) received HAART alone. 13 of these 15 (86%) died or were lost to follow-up before receiving chemotherapy. Patients randomized to CXT but not receiving chemotherapy had low baseline CD4 counts (median 77 cells/μL); compared to those receiving chemotherapy (median 249 cells/μL). Sixteen patients (31% of chemotherapy administered) received oral etoposide. Among patients receiving chemotherapy, the median number of cycles administered was 6 (inter quartile range 4-6). Five patients (4%) were lost to follow-up (Fig. 1).

Kaposi Sarcoma Outcomes

Primary outcome was KS response at month 12. In the CXT arm, nine (17%) had a CR and 26 (49%) had a PR for an ORR of 66%; 18 (34%) failed to respond. In the HAART arm, four (7%) had a CR and 19 (32%) had a PR for an ORR of 39%; 36 (61%) failed to respond. The absolute difference in ORR was 27% (95% CI 9-43%; Table 2). Limiting analysis to the 100 subjects with T1 disease, ORR was 64% in the CXT arm and 36% in the HAART arm (p=0.009, Fisher's Exact test).

One year PFS in the CXT arm was 56% vs. 31% in the HAART arm, hazard ratio (HR) = 0.52 (95% CI = 0.31, 0.88; Fig. 2a). Results were similar after limiting PFS analysis to T_1 patients (HR = 0.54, 95% CI = 0.31, 0.93) Furthermore, patients randomized to CXT obtained earlier tumor regression compared to HAART (TTR rate ratio 2.8 [95% CI 1.7, 4.4]; Fig. 2b). By as treated analysis, the proportion of patients receiving HAART alone that achieved PR or better at month 12 month was 38%; for those receiving HAART and at least one cycle of chemotherapy, it was 69% (74% for ABV, 56% for oral etoposide). (comparison of HAART to HAART and any chemotherapy, p=0.001, Fisher's exact test)

Overall Survival

Despite most patients being poor risk, 12-month OS was 77%, with no significant difference between arms (p=0.49; Figure 2c). This remained true after correcting for TIS risk factors (p=0.33), in a secondary as treated analysis (p=0.1), and when limiting analysis to T_1 subjects (OS = 74%, p=0.54). Of 26 deaths, 12 died of documented progressive KS (46% of deaths), 10 of these met criteria for KS-IRIS. Nine of the 12 (3 in the HAART arm and 6 in the CXT arm) died prior to receiving chemotherapy. Two additional patients with pulmonary KS died of respiratory symptoms of unknown aetiology. Two died of liver failure, 2 of documented infection, and 8 of other causes. Patient 12-month OS was evaluated based on the number of ACTG risk features. Multivariate logistic regression including established risk factors effectively risk-stratified patients (p=0.03), validating the modified ACTG staging system in our population. In this cohort in which 89% had T_1 disease, S_1 (including history of TB in 16 of 44 (36%) S_1 patients), emerged as the most

important TIS predictor of 12-month OS, with borderline statistical significance on multivariate analysis (univariate hazard ratio [HR] of death, S_1 compared to S_0 = 2.4, p=0.02; multivariate analysis, HR = 2.0, p=0.08). Baseline CD4 count <150 cells/μl was a less powerful predictor of 12 month OS (univariate HR of death for I_1 compared to I_0, = 1.9, p=0.1; multivariate analysis, HR = 1.6, p= 0.24) than using CD4 count <100 cells/uL as a cut-off (univariate HR of death for CD4 <100 cells/ul compared to ≥100 cells/uL = 2.6, p<0.01; multivariate analysis, HR = 2.74, p<0.01; TIS model using I_1 = CD4 <100 cells/uL, p<0.01)(Fig 2d). Additionally, female sex was an independent risk factor for death in univariate analysis (HR =2.6, p=0.02), and after correcting for other TIS risk factors, (CD4 <100 cell/uL cut-off), and treatment arm. (HR 2.6, p=0.04).

Adverse Events

The commonest severe adverse events (per patient) were abnormal liver function tests (16%), anemia (17%), and infections (22%). There were no statistically significant differences in the number and proportion of severe of adverse events between arms (Table 3). KS-IRIS (see Table, Supplemental Digital Content 2, definition of KS-IRIS) was diagnosed in 23 (21%) patients. Ten of these, including 9 with visceral KS, died. Pulmonary KS-IRIS contributed to 6 of these deaths. Overall, 37% of all deaths occurred in patients meeting criteria for KS-IRIS. There were no significant differences between arms in the occurrence or mortality attributed to KS-IRIS.

Adherence and HIV-related Outcomes

Seven-day recall was performed on 1070 of 1175 (91%) total visits. In the HAART arm, patients reported 100% adherence in 92.4% of visits, vs. 89.5% of visits in the CXT arm (p=0.8, Fisher's exact test). Seven patients (12%) in the HAART arm, and five (9%) in the CXT arm changed HAART due to toxicity or virologic failure. Two in the HAART arm were switched on two occasions. HIV virologic control was very good, with 82% of patients with HIV < 50 copies/ml at month 12 and no difference between arms (p=1.0). CD4 reconstitution was seen in most patients. In patients completing 12 months of follow up, median increase from baseline to month 12 was 129 cells/μL (range -185, +860) with no difference between arms (p=0.73) (see Figure, Supplemental Digital Content 3, median CD4 count and interquartile range: baseline, month 6, month 12, by arm).

Quality-of-Life

QOL improved significantly from baseline to month 12 on HAART. In the entire cohort, median global health score (perfect score = 100) was 50 at baseline and 67 at month 12 (p<0.001). CR or PR by month 12 was associated with increased global health score (p<0.001). Across subjects, improvements in emotional (p<0.001), social (p=0.003) and cognitive functioning (p<0.001) were noted. Symptom scales demonstrating statistically significant improvements (p<0.01) were: fatigue, appetite loss, pain, dyspnea, insomnia, constipation, diarrhea and financial problems. Comparing arms, a trend towards improved role functioning (perfect score = 100) favoured the CXT arm (median change HAART = 0, CXT = +17; p=0.011). Improvement in pain (perfect score = 0, median change HAART = -16.7, CXT = -33.3; p=0.1) and overall QOL (median change HAART = 12.5, CXT = 16.7; p=0.08) were also greater in the CXT arm. Comparisons between arms were not statistically significant.

Discussion

This is the first randomized controlled trial utilizing HAART in African patients with HIV-KS. We compared HAART alone to HAART combined with chemotherapy for KS efficacy, OS, safety, control of HIV, adherence and QOL improvement. Patients were treatment

naïve, 89% had advanced (but not immediately life threatening) KS and 58% had CD4 <200 cells/μL. This is the population most likely to be in need of therapy for both diseases in Africa. Randomization to CXT improved 12-month ORR (66% in CXT arm vs. 39% HAART arm). 77% of patients were alive at 12-months, and patients randomized to HAART alone had similar OS compared to those randomized to HAART and chemotherapy.

The KAART study provides much-needed randomized controlled trial evidence regarding therapy for HIV-KS in sub-Saharan Africa. 39% responded to HAART alone, providing the best estimate of efficacy of HAART alone in the treatment of HIV-KS treatment-naïve patients with advanced KS. ORR with HAART alone compares favourably to that seen in a Spanish study (ORR = 20%), despite a high proportion of T_1 patients in the KAART study (T_1 15% in the Spanish study vs. 89% in KAART),[7] perhaps reflective of differences in HIV resistance profiles, other unmeasured KS associated factors, and adherence. The ORR seen in the CXT arm (66%) is superior to a large Zimbabwean study, which administered ABV without the benefit of HAART (49%).[10]

Importantly we demonstrated excellent 12-month OS (77%) in this high-risk cohort, comparing favourably to the <40% 12-month OS noted in the Zimbabwean study[10] and in-line with OS estimates across a range of HIV-KS stages in industrialized countries (24 month OS 58% -84%)[8,12,21,22] after broad availability of HAART. In Africa, modified ACTG staging remains useful for prognosis in HIV-KS (p=0.03). Systemic illness is a significant prognostic factor of OS. History of tuberculosis was the commonest co-morbidity (36%), and management of concurrent KS and tuberculosis remains a particularly important challenge in sub-Saharan Africa. Active screening and therapy for tuberculosis are important steps to reduce morbidity and mortality of HIV-KS patients. HIV-KS patients with CD4 <100 cells/μL are also at an increased risk of dying in the first 12 months of therapy, and may require extra attention to supportive care.

While KAART demonstrates that HAART with or without chemotherapy improves 12-month OS in South African treatment-naïve patients with HIV-KS (77% versus 30-40% historical controls), additional studies are needed. KS-IRIS developed in 23 patients, and contributed to mortality in 10. Improved understanding of risk factors and underlying pathophysiology of KS-IRIS,[34,35] improved recognition and earlier use of chemotherapy as well as novel treatment strategies could lead to further improvements in survival for these high-risk patients.

KAART had a female preponderance, reflecting the HIV and HIV-KS epidemics in South Africa. Women had poorer 12-month survival not explained by ACTG prognostic factors or treatment arm. This finding builds on retrospective observations that women with HIV-KS have more aggressive disease and inferior outcomes than men[23-25], and is the first prospective study demonstrating inferior outcomes in women despite comparable therapy.

Notably, HIV and HIV-KS outcomes observed in KAART were obtained using a non-nucleoside reverse transcriptase inhibitor based regimen. Additional HAART regimens, including protease inhibitor based regimens, are now available in the public sector in South Africa. While controlling HIV[26] viremia and allowing for immune reconstitution[27] are the primary goals in using HAART to treat HIV-KS,[28-30] evaluation of additional anti-HHV-8 effects of specific antiretroviral agents remains an area of active research[31,32].

KAART is the first study to document influence of HAART, with or without chemotherapy, on QOL in patients with HIV-KS. Patients benefitted significantly in overall global health status, functioning and symptom scales. Most dramatic improvements were reported for pain, fatigue, insomnia, constipation and financial problems. There were no statistically

significant differences in QOL measures between arms; however obtaining PR or better was associated with improvement in global quality of life, validating tumor regression as an important palliative goal in advanced HIV-KS.[10,33]

A related question is whether addition of chemotherapy to HAART causes unnecessary toxicity or otherwise compromises HIV-directed care. Overall, the adverse event profile was manageable in both arms and not statistically different. The commonest adverse events experienced were: hepatitis, parasthesias, anemia, diarrhea, vomiting and pneumonia. The majority were grade 1-2 toxicities; severe toxicity rates did not differ significantly between arms. Given cross over between arms and the use of two separate chemotherapeutic regimens, the lack of difference of severe toxicities between arms should not be strictly interpreted. Patients receiving chemotherapy in addition to HAART for HIV-KS require monitoring for known chemotherapy specific adverse events. Larger studies are required to further define the toxicity profile of patients receiving chemotherapy for HIV-KS in sub-Saharan Africa. HAART regimen changes due to drug toxicity were noted in 8/112 (7%), the commonest being nevirapine hepatitis (4/122). Less common were peripheral neuropathy and anemia. Chemotherapy did not significantly worsen adherence. This is crucial, as high pill burden is an important issue in HIV-care in resource-limited settings. Patients likely benefited from frequent support in order to achieve and maintain adherence. CD4 increase and HIV-VL decay were comparable between arms.

A limitation of the study was that some patients randomized to CXT did not receive the intended ABV due to a variety of common problems with chemotherapy administration in sub-Saharan Africa. Despite this introduced heterogeneity, which would be expected to weaken findings in ITT analysis, being randomized to CXT had benefits with respect to tumor response. The number needed to treat (NNT) with chemotherapy in addition to HAART in order to obtain a partial response or better by 12 months was 3.7 (95% CI 2.2, 11.9). The NNT to prevent one patient from disease progression at six months was 3.3 (95% CI 2.3, 5.8). Importantly, findings from the KAART study may not be generalizable to HIV-KS patients with symptomatic visceral disease or fungating lesions. Furthermore, the KAART study was not designed to evaluate optimal chemotherapy in patients with HIV-KS. To address this, another randomized controlled trial of several chemotherapeutic regimens for African patients with advanced HIV-KS is planned (NCT01435018).

Conclusion

HAART is essential in improving survival in patients with HIV-KS in South Africa, while chemotherapy improves KS specific responses. HAART controls HIV, and may be sufficient in managing KS in a sizable proportion of treatment naïve HIV-KS patients, even those with T_1 disease. This is of particular importance given the current unavailability of chemotherapy in many African settings, where KS remains the commonest malignancy. Effective therapy for KS remains important goal for decreasing morbidity in African patients with HIV-KS. Chemotherapy has a benefical role in some HIV-KS patients, and the addition of chemotherapy to HAART results in improved ORR, TTR and PFS in HIV-KS. Further studies of KS-specific therapies combined with HAART are warranted for African patients with advanced HIV-KS as is more widespread availability and use of established chemotherapy for patients with symptomatic disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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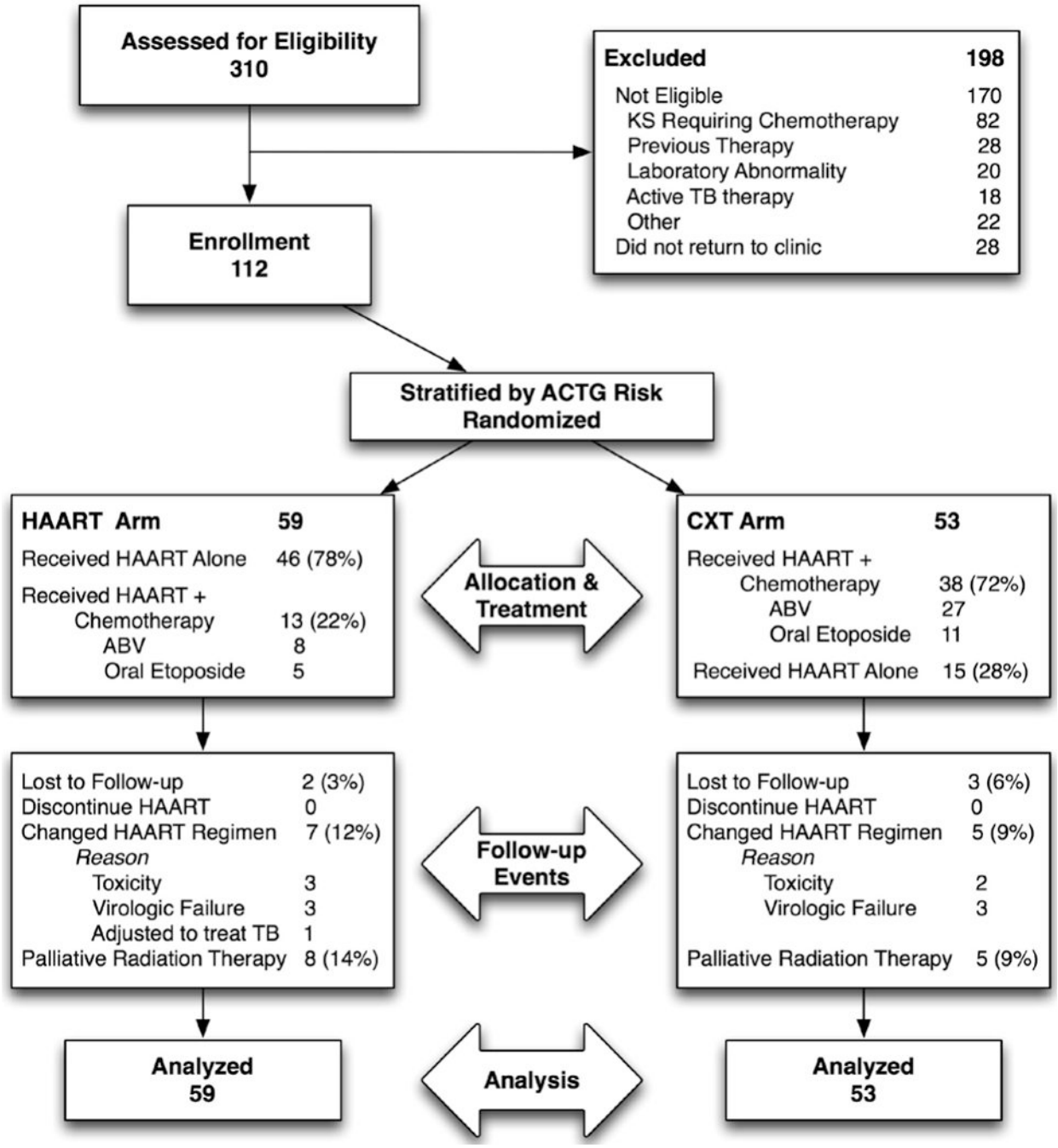

Figure 1. Patient Flow Chart: screening, randomization, follow-up events, and analysis

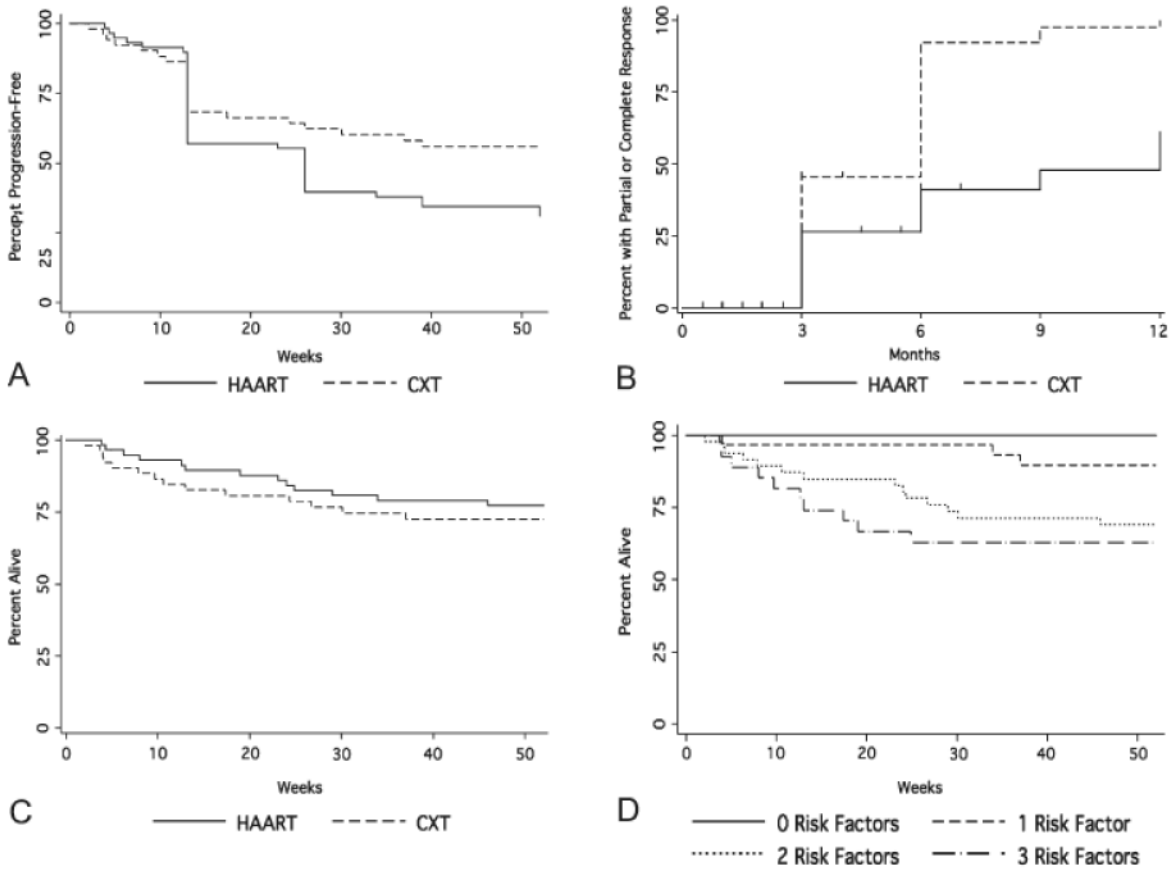

Figure 2. Progression-free Survival, Time to Response, and Overall Survival

a) Progression-free survival: Kaplan-Meier analysis, hazard ratio for progression in HAART plus chemotherapy (CXT) arm compared to HAART alone arm = 0.52 (95% CI = 0.31, 0.88, log-rank test).

b) Time to partial or complete response: based on three-monthly evaluations, patients censored (hatch marks) at time of death or loss to follow-up. Time to response rate ratio HAART arm compared to HAART plus chemotherapy (CXT) arm 2.8 (95% CI 1.7, 4.4, Mantel-Haenszel rate ratio)

c) Overall survival by arm: Kaplan-Meier analysis, CXT = HAART plus chemotherapy Difference between arms not significant (p=0.49, log-rank test), also not significant after correcting for TIS risk factors (p=0.33, Cox regression).

d) Overall survival by number (0-3) of modified ACTG TIS risk factors, (I_1 = CD4 less than 100 cells/mL): Kaplan-Meier analysis, multivariate Cox regression including modified ACTG risk factors effectively risk-stratified patients (p<0.01).

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Table 1

Baseline Patient Characteristics

Feature	HAART[a] n=59		CTX[b] n=53		p-value[c]
Age					
Median (Interquartile range)	34 (29 -39)		33 (28 -39)		0.6
	n	%	n	%	
Sex					1.0
Male	26	44%	24	45%	
Female	33	56%	29	55%	
Race					1.0
Black	57	96.6%	53	100%	
White	1	1.7%	0	0%	
Coloured	1	1.7%	0	0%	
Primary Language					0.01
English	7	12%	0	0%	
isZulu	52	88%	52	98%	
Other	0	0%	1	2%	
Residence					0.49
Urban	40	68%	37	70%	
Rural	19	32%	16	30%	
Stage					
T_1[d]	50	85%	50	94%	0.13
I_1[e]	31	53%	21	40%	0.19
S_1[f]	24	41%	20	38%	0.85
S_1 due to treated tuberculosis	9	15%	7	13%	0.72
ACTG = poor risk[g]	54	92%	50	94%	
CD4 (cells/μL)					
Median (Interquartile range)	136 (79 – 246)		192 (77 – 358)		0.29
% <200	37 (63%)		28 (53%)		0.34

Feature	HAART[a] n=59	CTX[b] n=53	p-value[c]
Log_{10} HIV viral load			
Median (Interquartile range)	4.98 (4.43 – 5.6)	4.94 (3.94 – 6.2)	0.86
% Undetectable	0%	0%	

[a] HAART: stavudine, lamivudine and nevirapine (Triomune®).

[b] CXT: HAART plus doxorubicin (20 mg/m^3), bleomycin (10 U/m^2), and vincristine (1.4 mg/m^2). Oral etoposide (50-100 mg days 1- 21 of a 28 day cycle)[16] was used as alternative therapy in event of difficulties with chemotherapy drug supply or intravenous administration during the protocol.

[c] Mann-Whitney test for comparison of medians, Fischer's exact test for comparison of proportions.

[d] T_1: Edema or ulceration, extensive oral mucosa KS, or visceral KS

[e] I_1: CD4 < 150 cells/μL

[f] S_1: History of opportunistic infections or thrush, “B” symptoms present, Karnofsky < 70 %, other HIV related disease

[g] ACTG poor risk = at least one T, I or S risk factor.

Table 2

12-Month Kaposi Sarcoma Response, Compared to Baseline by AIDS Clinical Trial Group Response Criteria

Arm 12 Month Response	HAART[a] (n=59) n (%) (95%CI)	CXT[b] (n=53) n (%) (95%CI)	Absolute Difference CXT – HAART (%) (95%CI)	p[c]
Overall Response	23 (39)	35 (66)	27	0.005
	(28, 52)	(53, 77)	(9, 43)	
Complete Response	4 (7)	9 (17)	10	0.14
	(2, 16)	(9, 29)	(-2, 23)	
Partial Response	19 (32)	26 (49)	17	0.08
	(22, 45)	(36, 62)	(-1, 34)	
Stable Disease	10 (17)	0 (0)	17	< 0.001
	(9, 28)	(0, 7)	(7, 28)	
Progressive Disease	11 (19)	1 (2)	17	< 0.001
	(11, 30)	(0, 10)	(5, 28)	
Deceased	13 (22)	14 (26)	4	0.66
	(13, 34)	(16, 40)	(-11, 20)	
Lost to Follow-up	2 (3)	3 (6)	2	0.67
	(1, 11)	(2, 15)	(-12, 6)	

[a] HAART: stavudine, lamivudine and nevirapine (Triomune®).

[b] CXT: HAART plus bleomycin (10 U/m^2), doxorubicin (20 mg/m^3), and vincristine (1.4 mg/m^2). Oral etoposide (50-100 mg days 1- 21 of a 28 day cycle)[16] was used as alternative therapy in event of difficulties with chemotherapy drug supply or intravenous administration during the protocol.

[c] Fisher's exact test

Table 3

Serious Adverse Events: DAIDS[a] Grade 3-5 Toxicities and Immune Reconstitution Syndrome; Intention to Treat, Worst Grade per Patient

Adverse Events	HAART[b] (n=59)			CXT[c] (n=53)			
Grade	3	4	5	3	4	5	p[d]
HEMATOLOGIC							
Anemia	9	3		3	4		0.45
Thrombocytopenia	1			2	2		0.19
DVT/PE[e]	1	1	1				0.25
CHEMISTRIES, FLUIDS, LIVER FUNCTION							
Elevated Creatinine	1						1.0
Hyponatraemia		1		4			0.19
Anasarca		1			2		0.6
LFT[f]/Hepatotoxicity	9	2	2	4	1		0.08
CARDIOVASCULAR							
Congestive Heart Failure			1				1.0
Hypertension			1				1.0
RESPIRATORY							
Dyspnea			1				1.0
Parasthesias				1			0.47
Encephalitis						1	0.47
CNS[g] Ischemia	1						1.0
INFECTIONS							
Tuberculosis	1				2		0.6
PCP[h]		1			1		1.0
Pneumonia	2		1	6	3		0.06
Cellulitis	4	1					0.06
Meningitis	1		1				0.5
Fever, Unknown Origin		1					1.0
IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME[i]							
Tuberculosis	1					1	1.0

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Adverse Events	HAART[b] (n=59)			CXT[c] (n=53)			
Grade	**3**	**4**	**5**	**3**	**4**	**5**	**p[d]**
Meningitis	1						1.0
KS	6	1	4	2	1	6	0.48

[a] Division of AIDS Table for grading the severity of adult and pediatric adverse events. Published December 2004. http://rcc.tech-res-intl.com

[b] HAART: stavudine, lamivudine and nevirapine (Triomune®).

[c] CXT was HAART plus bleomycin (10 U/m^2), doxorubicin (20 mg/m^3), and vincristine (1.4 mg/m^2). Oral etoposide (50 mg days 1- 21 of a 28 day cycle)[16] was used as alternative therapy in event of difficulties with chemotherapy drug supply or intravenous administration during the protocol.

[d] Comparison between groups for each AE (all grades) compared with Fisher's exact test, 2-sided p-value.

[e] DVT/PE: deep vein thrombosis, pulmonary embolism

[f] LFT: Liver function test abnormalities

[g] CNS: Central nervous system

[h] PCP: *Pneumocystis jiroveci* pneumonia

[i] Immune reconstitution inflammatory syndrome: a paradoxical deterioration in clinical status within the first 12 weeks of HAART due to a pre-existing antigen or pathogen, associated with >1 log decline in HIV-1 VL and/or CD4 improvement of > 30%.Additionally, KS-IRIS required a rapid progression of KS disease inconsistent with its natural history; which is evident by rapid progression of existing lesions and/or tumor associated edema and/or dramatic development of new KS-lesions. IRIS symptoms cannot be attributable to a newly acquired infection, uncontrolled known infection, or a side affect of a new medication