



A5263/AMC066

**Randomized Comparison of Three Regimens of
Chemotherapy with Compatible Antiretroviral
Therapy for Treatment of Advanced AIDS-KS in
Resource-Limited Settings**

**A Multicenter Trial of the AIDS Clinical Trials
Group (ACTG)**

And

AIDS Malignancy Consortium (AMC)

DAIDS ES # 10724

This file contains the current ACTG A5263/AMC066 protocol, which includes the following documents:

- Letter of Amendment #2, dated 11 June 2018
- Letter of Amendment #1, date 8 February 2018
- Protocol Version 3.0, dated 7 December 2016

Letter of Amendment #2 for:

A5263/AMC066

**Randomized Comparison of Three Regimens of Chemotherapy with Compatible
Antiretroviral Therapy for Treatment of Advanced AIDS-KS in Resource-Limited Settings**

A Limited Center Trial of the AIDS Clinical Trials Group (ACTG)

And

AIDS Malignancy Consortium (AMC)

DAIDS ES # 10724

Letter of Amendment Date: 11 June 2018

ACTG Network Coordinating Center

Social & Scientific Systems, Inc.

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Silver Spring, MD 20910*

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LETTER OF AMENDMENT

DATE: June 11, 2018

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5263/AMC066 Protocol Team

SUBJECT: Letter of Amendment #2 for Protocol A5263/AMC066, Version 3.0, 12/07/16,
entitled, "Randomized Comparison of Three Regimens of Chemotherapy with
Compatible Antiretroviral Therapy for Treatment of Advanced AIDS-KS in
Resource-Limited Settings"

**The following information affects the A5263/AMC066 study and must be forwarded to
your institutional review board (IRB)/ethics committee (EC) as soon as possible for their
information and review. This Letter of Amendment (LOA) must be approved by your
IRB/EC before implementation.**

**The following information may also affect the Sample Informed Consent. Your IRB/EC is
responsible for determining the process of informing participants of the contents of this
LOA.**

**Upon receiving final IRB/EC and any other applicable regulatory entity approvals for this
LOA, sites should implement the LOA immediately. Sites are still required to submit an**

LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all required LOA registration documents have been received and are complete. An LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification, along with this letter and any IRB/EC correspondence, should be retained in the site's regulatory files.

The following are changes to A5263/AMC066, Version 3.0, 01/05/16 (changes are noted in bold or strikethrough).

The NIAID DAIDS Co-Infections and Complications Data and Safety Monitoring Board (DSMB) met on March 13, 2018 to review safety and efficacy data from the A5263/AMC066 study. The DSMB recommended that A5263/AMC066 be stopped because the bleomycin/vincristine arm was inferior to the paclitaxel arm when the primary composite endpoint was evaluated. No safety concerns were identified. The DSMB made the following recommendations:

1. The DSMB recommends stopping the study. The information at this interim analysis show that conclusions that can be made from this study at the current time will change little even if the study were continued to the end. The current statements that can be made about the two treatment arms are scientifically solid and important, and it is important to disseminate the results as soon as possible.
2. The study team should develop a plan to offer paclitaxel to patients who are currently on the study.

To achieve recommendation #2, the team has developed a table that describes options for participants currently on study treatment in A5263/AMC066. This table is attached for reference as Appendix I. The protocol has been minimally changed to implement this table; therefore, only minimal edits are included in this LOA.

The following are changes (noted in bold font and strikethrough) to A5263/AMC066, Version 3.0, 12/07/16:

1. SCHEMA, DURATION

Participants randomized to receive paclitaxel (PTX) in Step 1

- **Participants who have not already done so should complete their current course (up to 6 cycles) of study-provided PTX chemotherapy and study-provided ART.**
- **Once participants have completed step 1 chemotherapy, they must permanently transition to local ART care as soon as it can be arranged, but not later than 90 days after completion of Step 1 chemotherapy.**
 - **Participants on study at a site where PTX is not available for free to the participant should be followed on study to determine if they are eligible to receive PTX (up to 6 cycles) in Step 2. If participants become ineligible for Step 2, participants must permanently transition to locally provided oncology care as soon as it can be arranged, but not later than 90 days, and then go off study.**
 - **Participants on study at a site where PTX is available for free to the participant must permanently transition to locally provided oncology care as soon as it can be arranged, but not later than 90 days, and then go off study.**

Participants randomized to receive paclitaxel (PTX) in Step 2 or Step 3

- Participants should complete their current course (up to 6 cycles) of chemotherapy and study-provided ART then permanently transition to local care as soon as appropriate oncology and ART care can be arranged, but not later than 90 days, and then go off study.

Participants randomized to receive bleomycin plus vincristine (BV) in Step 1 or Step 2 who choose to switch to PTX

- Participants on study at a site where PTX is not available for free to the participant may receive study-provided PTX (up to 6 cycles) and ART on Step 3, as long as eligibility criteria for PTX are met. After completion of all cycles of PTX, participants must permanently transition to local care as soon as appropriate oncology and ART care can be arranged, but not later than 90 days, and then go off study.
- Participants on study at a site where PTX is available for free to the participant must permanently transition to locally provided PTX as soon as it can be arranged along with appropriate ART care, but not later than 90 days, and then go off study.

Participants randomized to receive BV in Step 1 or Step 2 who choose not to switch to PTX at this time

- Participants who have not already done so should complete their current course (up to 6 cycles) of study-provided BV chemotherapy and study provided ART.
- Once study-provided BV is complete, participants must permanently transition to local ART care as soon as it can be arranged, but not later than 90 days after completion of study-provided BV.
- Participants may continue to be followed up to week 72 (or R+48, whichever comes first) or until the decision is made to switch their chemotherapy to PTX (this decision can be made up to week 72). At this time:
 - Participants on study at a site where PTX is not available for free to the participant may receive study-provided PTX (up to 6 cycles) on Step 3. After completion of all cycles of PTX, participants must permanently transition to locally provided oncology care as soon as it can be arranged, but not later than 90 days, and then go off study.
 - Participants on study at a site where PTX is available for free to the participant must permanently transition to locally provided oncology care as soon as it can be arranged, but not later than 90 days, and then go off study.

Participants no longer eligible to receive study-provided chemotherapy

- Permanently transition to local care as soon as appropriate oncology and ART care can be arranged, but not later than 90 days, and then go off study.

Participants who received etoposide (ET) while on study

Participants will be followed for 144 weeks after beginning the last cycle of ET. ~~All other participants will be followed for 96 weeks after randomization or assignment to the last step they enter.~~

~~For participants who did not receive ET while on study, the duration of follow-up will be as follows:~~

- ~~• Participants who are randomized ONLY to Step 1 and who do not enter Step 2 or 3 will be followed for 96 weeks from Step 1 entry;~~
- ~~• Participants who are randomized to Step 2 and/or 3 will be followed for 48 weeks after entry into the last step that they enter.~~

2. Section 3.0, STUDY DESIGN

Participants who received etoposide (ET) while on study will be followed for 144 weeks after beginning the last cycle of ET. All other participants will be followed for 96 weeks after randomization or assignment to the last step they enter.

~~For participants who did not receive ET while on study, the duration of follow-up will be as follows:~~

- ~~• Participants who are randomized ONLY to Step 1 and who do not enter Step 2 or 3 will be followed for 96 weeks from Step 1 entry;~~
- ~~• Participants who are randomized to Step 2 and/or 3 will be followed for 48 weeks after entry into the last step that they enter.~~

3. Section 4.3, Inclusion Criteria Step 2

4.3.1 ~~IERC-Confirmed~~ complete response (CR) or partial response (PR) to the **PTX** in Step 1.

4.3.2 ~~IERC-confirmed~~ KS progression at least 12 weeks after the last dose of Step 1 **PTX**.

4. Section 4.4, Exclusion Criteria Step 2

4.4.10 Receipt of BV in Step 1.

5. Section 4.5, Inclusion Criteria Step 3

4.5.1 ~~IERC-confirmed~~ KS progression at any time during Step 1 chemotherapy OR

- ~~IERC-confirmed~~ KS progression fewer than 12 weeks after the last chemotherapy dose in Step 1 in participants who have had an ~~IERC-confirmed~~ CR or PR OR
- ~~IERC-confirmed~~ KS progression following Step 1 chemotherapy, without any prior response OR
- ~~IERC-confirmed~~ KS progression in Step 2 OR
- With concurrence of the CMC, there is dose-limiting toxicity after receiving fewer than four cycles of chemotherapy in Step 1 or Step 2, in the absence of a CR or PR OR
- Participants otherwise eligible for Step 2 who, in the opinion of the investigator and with concurrence of the CMC, are unlikely to benefit from another course of the same chemotherapy received in Step 1.
- Receipt of BV in Step 1 or Step 2.**

6. Section 4.6, Exclusion Criteria Step 3

4.6.9 Receipt of PTX in Step 1 and/or Step 2.

7. Section 5.0, STUDY TREATMENT

Participants will have access to local standard of care ART and chemotherapy through local treatment programs available at the sites following **discontinuation of study-provided treatment study week 96**. As part of their site implementation plan (SIP), sites are required to demonstrate that they have developed the appropriate relationship with local treatment programs to provide the local standard of care for ART and chemotherapy. Please refer to the A5263/AMC066 PSWP for the detailed SIP.

8. Section 5.1.1.5, Antiretroviral Therapy

The study will provide ART **while participants are receiving study-provided chemotherapy, unless they have already transitioned to local ART care. Once participants have completed study-provided chemotherapy, they must permanently transition to local ART care as soon as it can be arranged, but not later than 90 days after completion of study-provided chemotherapy.**

Alternatively, sites may choose at any time to transfer a participant's ART to locally provided drugs. ~~until week 96 after Step 1 Randomization.~~

9. **Section 6.1.1, CLOSEOUT Schedule of Evaluations, Step 1 – Screening to Week 24**

Evaluation	Step 1 Post-Entry Evaluations (Weeks)									Virologic Failure	KS-IRIS
	3 ^{3,4}	24–48 Hours after Second Chemotherapy Cycle Begins	6 ^{3,4}	9 ^{3,4}	12 ^{3,4}	15 ^{3,4}	18 ^{3,4}	21 ^{3,4}	24 ^{3,4}		
Concomitant Medications	X		X	X	X	X	X	X	X		X
Complete Physical Exam											
Body Surface Area Calculation	Recalculate if a participant's weight has changed by 10% or more after Step 1 entry for re-calculation of bleomycin and PTX doses										
Targeted Physical Exam	X		X	X	X	X	X	X	X		X
Clinical Assessment	X		X	X	X	X	X	X	X		X
KS Exam	X		X	X	X	X	X	X	X		X
CD4+/CD8+ (for participants on study-provided ART)					X				X		X
HIV-1 RNA (for participants on study-provided ART)					X				X	X	X
Hematology	X		X	X	X	X	X	X	X		
Chemistries	X		X	X	X	X	X	X	X		
Lactate											
Lipase & Triglycerides											
Creatine Kinase											
Pregnancy Testing	Perform prior to a new chemotherapy cycle and whenever pregnancy is suspected										
CXR											X
Pulse Oximetry	X ²		X ²	X ²	X ²	X ²	X ²	X ²	X ²		

² Complete only if the participant is receiving bleomycin.

³ Evaluations are required every 3 weeks if participants are receiving study-provided chemotherapy.

⁴ Evaluations are required every 6 weeks if participants are not receiving study-provided chemotherapy. Q6 week visits should commence at the next even-numbered study week after completing chemotherapy.

10. Section 6.1.2, CLOSEOUT Schedule of Evaluations, Step 1 – Week 27 to Discontinuation Evaluations

Evaluation	Step 1 Post-Entry Evaluations (Weeks)										Discontinuation Evaluations	Virologic Failure
	27 ^{5,6}	30 ^{5,6}	33 ^{5,6}	36 ^{5,6}	39 ^{5,6}	42 ^{5,6}	45 ^{5,6}	48 ^{5,6}	60-96 (Follow-up Every 12 Weeks) ²	E + 144 ³		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Targeted Physical Exam	X	X	X	X	X	X	X	X	X		X	
Clinical Assessment	X	X	X	X	X	X	X	X	X	X	X	
KS Exam	X	X	X	X	X	X	X	X	X		X	
CD4+/CD8+ (for participants on study-provided ART)				X				X	X		X	
HIV-1 RNA (for participants on study-provided ART)				X				X	X		X	X
Hematology	X			X				X	X	X	X	
Chemistries	X			X				X	X		X	
Lactate	Perform for symptoms suggestive of lactic acidosis											
Lipase & Triglycerides	Perform for symptoms suggestive of pancreatitis											
Creatine Kinase	Perform for symptoms suggestive of myopathy											
Pregnancy Testing	Perform prior to a new chemotherapy cycle and whenever pregnancy is suspected										X	
CXR	Repeat at the time of suspected or IERC-confirmed KS progression or entry into the next step. For participants with known pulmonary KS at entry, a CXR will be repeated on every third cycle.											
Pulse Oximetry	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	

² If conducted on Step 1, week 96 is the last visit for participants in Arm 1B or 1C.

³ E=week the last cycle of ET was started. The E+144 visit will only be conducted for participants in Arm 1A who are still on Step 1.

⁴ Complete only if the participant is receiving bleomycin.

⁵ Evaluations are required every 3 weeks if participants are receiving study-provided chemotherapy.

⁶ Evaluations are required every 6 weeks if participants are not receiving study-provided chemotherapy. Q6 week visits should commence at the next even-numbered study week after completing chemotherapy.

11. Section 6.1.3, CLOSEOUT Schedule of Evaluations, Step 2, Step 3, and Step 4 – Randomization to Week 27

Evaluation	Entry (R)	Step 2 Post-Entry Evaluations (Weeks)										Virologic Failure
		R + 3 ^{4,5}	24–48 Hours after Second Chemotherapy Cycle Begins	R + 6 ^{4,5}	R + 9 ^{4,5}	R + 12 ^{4,5}	R + 15 ^{4,5}	R + 18 ^{4,5}	R + 21 ^{4,5}	R + 24 ^{4,5}	R + 27 ^{4,5}	
Concomitant Medications	X	X		X	X	X	X	X	X	X	X	
Targeted Physical Exam	X	X		X	X	X	X	X	X	X	X	
Body Surface Area Calculation	Recalculate if a participant's weight has changed by 10% or more after Step 1 entry for re-calculation of bleomycin and PTX doses											
Clinical Assessment	X	X		X	X	X	X	X	X	X	X	
KS Exam	X	X		X	X	X	X	X	X	X	X	
CD4+/CD8+ (for participants on study-provided ART)	X					X				X		
HIV-1 RNA (for participants on study-provided ART)	X									X		X
Hematology	X	X		X	X	X	X	X	X	X	X	
Chemistries	X	X		X	X	X	X	X	X	X	X	
Lactate	Perform for symptoms suggestive of lactic acidosis											
Lipase & Triglycerides	Perform for symptoms suggestive of pancreatitis											
Creatine Kinase	Perform for symptoms suggestive of myopathy											
Pregnancy Testing	Perform prior to a new chemotherapy cycle and whenever pregnancy is suspected											
CXR	Repeat at the time of suspected or IER-confirmed KS progression or entry into the next step. For participants with known pulmonary KS at entry or at the time of entry into Step 2 or Step 3, a CXR will be repeated on every third cycle.											
Pulse Oximetry	X ³	X ³		X ³	X ³	X ³	X ³	X ³	X ³	X ³	X ³	

³ Complete only if the participant is receiving bleomycin.

⁴ Evaluations are required every 3 weeks if participants are receiving study-provided chemotherapy.

⁵ Evaluations are required every 6 weeks if participants are not receiving study-provided chemotherapy. Q6 week visits should commence at the next even-numbered R+visit week after completing chemotherapy.

12. Section 6.1.4, CLOSEOUT Schedule of Evaluations, Step 2, Step 3, and Step 4 – Week 30 to Discontinuation Evaluations

Evaluation	Step 2, 3, and 4 Post-Entry Evaluations (Weeks)								Discontinuation Evaluations	Virologic Failure	
	R + 30 ^{4,5}	R + 33 ^{4,5}	R + 36 ^{4,5}	R + 39 ^{4,5}	R + 42 ^{4,5}	R + 45 ^{4,5}	R + 48 ^{4,5}	For Participants Who Received ET During Any Step R+60 — R+96 (Follow-up Every 12 Weeks)			E + 144 ²
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
Targeted Physical Exam	X	X	X	X	X	X	X	X		X	
Clinical Assessment	X	X	X	X	X	X	X	X	X	X	
KS Exam	X	X	X	X	X	X	X	X		X	
CD4+/CD8+ (for participants on study-provided ART)			X				X	X		X	
HIV-1 RNA (for participants on study-provided ART)			X				X	X		X	X
Hematology			X				X	X	X	X	
Chemistries			X				X	X		X	
Lactate	Perform for symptoms suggestive of lactic acidosis										
Lipase & Triglycerides	Perform for symptoms suggestive of pancreatitis										
Creatine Kinase	Perform for symptoms suggestive of myopathy										
Pregnancy Testing	Perform prior to a new chemotherapy cycle and whenever pregnancy is suspected									X	
CXR	Repeat at the time of suspected or IER-confirmed KS progression or entry into the next step. For participants with known pulmonary KS at entry or at the time of entry into Step 2 or Step 3, a CXR will be repeated on every third cycle.										
Pulse Oximetry	X ³	X ³	X ³	X ³	X ³	X ³	X ³	X ³	X ³	X ³	

² E=week the last cycle of ET was started. E+144 visit is only for participants who received ET while on study and have already completed the week R+96 visit on the last step entered.

³ Complete only if the participant is receiving bleomycin.

⁴ Evaluations are required every 3 weeks if participants are receiving study-provided chemotherapy.

⁵ Evaluations are required every 6 weeks if participants are not receiving study-provided chemotherapy. Q6 week visits should commence at the next even-numbered R+visit week after completing chemotherapy.

13. **Section 6.3, Instructions for Evaluations (new first paragraph)**

Upon implementation of this LOA, only evaluations noted in the CLOSEOUT Schedules of Evaluations are required.

14. **Section 7.1, KS Progression**

Please refer to the A5263/AMC066 MOPS for detailed information on calculating response categories and for the definition and instructions on evaluating non-measurable (evaluable) disease.

~~For purposes of this study, IERC confirmed KS progression is defined as KS progression that has been verified by the IERC. It is required that all KS progression be confirmed by the IERC. Changes in chemotherapy cannot occur until the site has received confirmation from the IERC. Please refer to the A5263/AMC066 MOPS for detailed instructions on contacting the IERC.~~

15. **Appendix VI, SAMPLE INFORMED CONSENT, WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?**

Anti-HIV and anti-cancer drugs after the study:

If you are not receiving study-provided chemotherapy, study visits to 96-72 weeks after Step 1 entry, the study will no longer provide you with anti-HIV or anti-cancer drugs. At that time, you may have to stop a drug combination that has worked well for you, either because you cannot afford the treatment or because those drugs are not available in your country. **The doctors at your site will make sure that you have appropriate local cancer and HIV care before you are taken off study.** ~~Efforts will be made by your doctor to find a way to continue anti-HIV and anti-cancer drugs after the study is over.~~

16. **Protocol Signature Page**

A Protocol Signature Page (PSP) is appended for submission to DAIDS Protocol Registration System (DPRS) as part of the LOA registration packet.

The information above will be incorporated into the next protocol version as necessary if the protocol is amended.

APPENDIX 1: CHEMOTHERAPY OPTIONS FOR PARTICIPANTS CURRENTLY ON STUDY TREATMENT

CURRENT STEP 1 TREATMENT	STEP 1 OPTION	STEP 2 OPTION*	STEP 3 OPTION*
Receiving paclitaxel or completed 6 cycles	Complete 6 cycles of paclitaxel (if not already complete)	1) If PR or CR and then progresses for up to week 72 of the protocol, may move to Step 2 for up to 6 more cycles 2) If criteria for PR or CR are not met during Step 1, no additional study treatment	NONE
Receiving BV or completed 6 cycles	If deriving some benefit (which could be having stable disease when KS was previously progressing) may continue with BV or have option to immediately enter Step 3 to receive paclitaxel	NONE	1) If choice is made to continue BV, option to receive paclitaxel later should be available up to study week 72. May then move to Step 3 with paclitaxel for up to 6 additional cycles, then no more study treatment. 2) If choice is made to immediately receive paclitaxel, may move to Step 3 with paclitaxel for up to 6 additional cycles, then no more study treatment
	If not deriving benefit, must discontinue BV and have option to enter Step 3 to receive paclitaxel	NONE	May receive 6 cycles of paclitaxel, then no additional study treatment

* Any move to Step 2 or Step 3 must be made by week 72 after entry onto the protocol.

CURRENT STEP 2 TREATMENT	STEP 2 OPTION	STEP 3 OPTION*
Paclitaxel	Complete 6 cycles, then no additional study treatment	NONE

Receiving BV or completed 6 cycles	If deriving some benefit (which could be having stable disease when KS was previously progressing) may continue with BV or have option to immediately enter Step 3 to receive paclitaxel	1) If choice is made to continue BV, option to receive paclitaxel later should be available up to study week 72 (or 48 weeks after randomization to Step 2 (i.e., study week R+48), whichever comes first). May then move to Step 3 with paclitaxel for up to 6 additional cycles, then no more study treatment. 2) If choice is made to immediately receive paclitaxel, may move to Step 3 with paclitaxel for up to 6 additional cycles, then no more study treatment
	If not deriving benefit, must discontinue BV and have option to enter Step 3 to receive paclitaxel	May receive 6 cycles of paclitaxel, then no additional study treatment

* Any move to Step 2 or Step 3 must be made by week 72 after entry onto the protocol.

CURRENT STEP 3 TREATMENT	STEP 3 OPTION*	STEP 4 OPTION*
Paclitaxel	Complete 6 cycles, then no additional study treatment	No additional options
BV	If deriving some benefit (which could be having stable disease when KS was previously progressing) may continue with BV	No additional options
	Otherwise, discontinue treatment and return to SOC	

* Any move to Step 2 or Step 3 must be made by week 72 after entry onto the protocol.

Randomized Comparison of Three Regimens of Chemotherapy with Compatible Antiretroviral
Therapy for Treatment of Advanced AIDS-KS in Resource-Limited Settings

SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

Letter of Amendment #1 for:

A5263/AMC066

Randomized Comparison of Three Regimens of Chemotherapy with Compatible Antiretroviral Therapy for Treatment of Advanced AIDS-KS in Resource-Limited Settings

A Limited Center Trial of the AIDS Clinical Trials Group (ACTG)

And

AIDS Malignancy Consortium (AMC)

DAIDS ES # 10724

Letter of Amendment Date: 8 February 2018

ACTG Network Coordinating Center

Social & Scientific Systems, Inc.

*8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910*

Phone: (301) 628-3000

Fax: (301) 628-3302

LETTER OF AMENDMENT

DATE: February 8, 2018

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5263/AMC066 Protocol Team

SUBJECT: Letter of Amendment #1 for Protocol A5263/AMC066, Version 3.0, 12/07/16, entitled, "Randomized Comparison of Three Regimens of Chemotherapy with Compatible Antiretroviral Therapy for Treatment of Advanced AIDS-KS in Resource-Limited Settings"

The following information affects the A5263/AMC066 study and must be forwarded to your institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This Letter of Amendment (LOA) must be approved by your IRB/EC before implementation.

The following information may also affect the Sample Informed Consent. Your IRB/EC is responsible for determining the process of informing participants of the contents of this LOA.

Upon receiving final IRB/EC and any other applicable regulatory entity approvals for this LOA, sites should implement the LOA immediately. Sites are still required to submit an LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all required LOA registration documents have been received and are complete. An LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification, along with this letter and any IRB/EC correspondence, should be retained in the site's regulatory files.

The following are changes to A5263/AMC066, Version 3.0, 12/07/16:

1. Schema, Title

The protocol title in the Schema has been revised to read:

A-Randomized Comparison of Three Regimens of Chemotherapy with Compatible Antiretroviral Therapy for Treatment of Advanced AIDS-KS in Resource-Limited Settings

2. Schema, Duration

This section has been revised to read:

Participants who received etoposide (ET) while on study will be followed for 144 weeks after beginning the last cycle of ET. ~~All other participants will be followed for 96 weeks after randomization or assignment to the last step they enter.~~

For participants who did not receive ET while on study, the duration of follow-up will be as follows:

- **Participants who are randomized ONLY to Step 1 and who do not enter Step 2 or 3 will be followed for 96 weeks from Step 1 entry;**
- **Participants who are randomized to Step 2 and/or 3 will be followed for 48 weeks after entry into the last step that they enter.**

3. Schema, Population

This section has been revised to read:

HIV-infected men and women with the following characteristics:

- Biopsy diagnostic of KS
- Naïve to ART ~~(as defined in section 4.2.7)~~, chemotherapy, and radiation therapy
- KS stage T1, (see section 4.1.3)
- Persons with chronic, acute, or recurrent infections that are serious, in the opinion of the site investigator, must have completed at least 14 consecutive days of appropriate anti-infective treatment prior to study entry and be clinically stable

4. Section 3, Study Design

The final paragraph has been revised to read:

Participants who received etoposide (ET) while on study will be followed for 144 weeks after beginning the last cycle of ET. ~~All other participants will be followed for 96 weeks after randomization or assignment to the last step they enter.~~

For participants who did not receive ET while on study, the duration of follow-up will be as follows:

- **Participants who are randomized ONLY to Step 1 and who do not enter Step 2 or 3 will be followed for 96 weeks from Step 1 entry;**
- **Participants who are randomized to Step 2 and/or 3 will be followed for 48 weeks after entry into the last step that they enter.**

5. Section 4.1, Inclusion Criteria Step 1

The following inclusion criterion has been added:

4.1.14 If currently on ART for ≥ 24 weeks prior to study entry, plasma HIV-1 RNA ≤ 400 copies/mL within 30 days prior to entry.

NOTE: Viral load suppression is not needed if participant is not currently on ART or has been on ART for less than 24 weeks prior to study entry. There is no limit on length of time of prior ART use.

6. Section 4.2, Exclusion Criteria Step 1

The following exclusion criterion has been removed:

~~4.2.7 Receipt of ART for more than 42 days immediately prior to entry. ART is allowed within the 42-day window prior to study entry.~~

~~NOTE: The use of single-dose nevirapine (NVP) or zidovudine (ZDV) for any period of time during pregnancy to prevent mother-to-child transmission (MTCT) of HIV is allowed.~~

~~NOTE: Successful post-exposure prophylaxis is allowed. Unsuccessful post-exposure prophylaxis is not allowed.~~

7. Section 4.2, Exclusion Criteria Step 1

Exclusion criteria 4.2.8-4.2.16 have been renumbered to **4.2.7-4.2.15**.

8. Section 5.1.1, Step 1

At entry, participants will be randomized in a 1:1 ratio to receive ART with **either EFV/FTC/TDF (Atripla®) or their current, effective, non-study-supplied ART regimen** plus either treatment regimen 1B or 1C as listed below.

9. Section 5.1.1.5, Antiretroviral Therapy

The study will provide ART until week 96 after Step 1 Randomization.

The study will provide EFV/FTC/TDF (Atripla®), which is the preferred ART regimen. If there is a contraindication to EFV, participants must have access to an alternative NNRTI or protease inhibitor/ritonavir (PI/r) provided from outside of the study.

The following ART regimens may be used:

- EFV/FTC/TDF (Atripla®) 200 mg/300 mg/600 mg orally once daily on an empty stomach, preferably at bedtime OR
- FTC/TDF 200 mg/300 mg (Truvada®) orally once daily at bedtime plus EFV (Stocrin®) 600 mg orally once daily at bedtime OR
- FTC/TDF 200 mg/300 mg (Truvada®) orally once daily plus NVP 200 mg orally twice daily OR
- FTC/TDF 200 mg/300 mg (Truvada®) orally once daily plus PI/r at standard dosing **OR**
- **FTC/TDF 200 mg/300 mg (Truvada®) orally once daily plus integrase inhibitor at standard dosing**

10. Section 5.4.1.3, Study Product Supply

Vincristine sulfate injection ~~manufactured by Hospira~~ is supplied through the study with funding support from the ACTG.

In the event that vincristine is not available through the study, locally sourced vincristine may be used until study provided vincristine is available. Locally sourced vincristine must first be approved by the A5263 CMC prior to administering it to any study participant in A5263. Any study product not provided by the study must comply with the NIAID (DAIDS) policy that outlines the process for authorizing the use of study products not marketed in the US in NIAID (DAIDS)-supported and/or sponsored clinical trials. This policy is available on the NIAID (DAIDS) website at: <https://www.niaid.nih.gov/sites/default/files/NonFDAApprovedProducts.pdf>.

Vincristine locally sourced by the site must be at a concentration of 1 mg/mL injectable solution in a vial for single use. The product must be prepared per protocol and stored as directed by the manufacturer in the package insert.

When a site switches from locally obtained vincristine (approved by the A5263 CMC) to vincristine provided through the study, the site must notify the A5263 CMC per instructions in the Study Management section of the protocol and document the date that use of vincristine provided through the study via the CRPMC is implemented at the site.

Site pharmacists are required to maintain complete records of study products received from the CRPMC and all other sources.

11 Section 6.1.4, Step 2, Step 3, and Step 4–Week 30 to Discontinuation Evaluations

This section has been revised as follows:

Evaluation	Step 2, 3, and 4 Post-Entry Evaluations (Weeks)							For Participants Who Received ET During Any Step R+60 — R+96 (Follow-up Every 12 Weeks)	E + 144 ²	Discontinuation Evaluations	Virologic Failure
	R + 30	R + 33	R + 36	R + 39	R + 42	R + 45	R + 48				
Biopsy Diagnostic of KS (Fixed in Formalin)	Repeat a diagnostic biopsy for KS to confirm a complete KS response ¹										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
Targeted Physical Exam	X	X	X	X	X	X	X	X		X	
Clinical Assessment	X	X	X	X	X	X	X	X	X	X	
KS Exam	X	X	X	X	X	X	X	X		X	
Photographic Record	Complete for a change in KS response category									X	
CD4+/CD8+			X				X	X		X	
HIV-1 RNA			X				X	X		X	X
Stored Serum, Plasma, PBMC for Protocol-Related Research							X			X	
Hematology			X				X	X	X	X	
Chemistries			X				X	X		X	
Lactate	Perform for symptoms suggestive of lactic acidosis										
Lipase & Triglycerides	Perform for symptoms suggestive of pancreatitis										
Creatine Kinase	Perform for symptoms suggestive of myopathy										
Urinalysis										X	
Pregnancy Testing	Perform prior to a new chemotherapy cycle and whenever pregnancy is suspected									X	
CXR	Repeat at the time of suspected or IERC-confirmed KS progression or entry into the next step. For participants with known pulmonary KS at entry or at the time of entry into Step 2 or Step 3, a CXR will be repeated on every third cycle.										
Pulse Oximetry	X ³	X ³	X ³	X ³	X ³	X ³	X ³	X ³	X ³	X ³	
ART Adherence Assessment	X						X	X		X	
Quality of Life Assessment							X			X	

¹ A confirmatory biopsy is required only for participants in whom hyperpigmented macular skin lesions persist after apparent CR.

² E=week the last cycle of ET was started. E+144 visit is only for participants who received ET while on study and have already completed the week R+96 visit on the last step entered.

³ Complete only if the participant is receiving bleomycin.

12. Section 6.2.2.2, Post-Entry, Steps 2, 3, and 4

This section has been revised to read:

Steps 2, 3, and 4

Study visits must be scheduled on the weeks indicated in the SOE ± 7 days for the step randomization visit to week R+48.

For participants who received ET during any Step: Study visits must be scheduled on the weeks indicated in the SOE, ± 14 days for the week R+60 visit to week R+96.

Study visits must be scheduled on the weeks indicated in the SOE ± 12 weeks for the E+144 visit.

13. Section 6.2.2.3.5, Long-Term Safety Follow-Up

This section has been revised to read:

Participants who received etoposide (ET) while on study will be followed for 144 weeks after beginning the last cycle of ET. ~~All other participants will be followed for 96 weeks after randomization or assignment to the last step they enter.~~

For participants who did not receive ET while on study, the duration of follow-up will be as follows:

- **Participants who are randomized ONLY to Step 1 and who do not enter Step 2 or 3 will be followed for 96 weeks from Step 1 entry;**
- **Participants who are randomized to Step 2 and/or 3 will be followed for 48 weeks after entry into the last step that they enter.**

14. Section 6.3, Instructions for Evaluations

This section has been revised to read:

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS website for information about what must be included in the source documents:

<https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.pdf>.

15. Section 6.3.6, Concomitant Medications

The fourth paragraph of this section has been revised to read:

After week 96 (or R+~~96~~**48** for participants who enter step 2, 3, or 4), only chemotherapy or radiation should be recorded in the CRF and source documents.

16. Section 9.1, General Design Issues

The last paragraph of this section has been revised to read:

Participants who received ET while on study (see protocol version 2.0) will be followed for 144 weeks after beginning the last cycle of ET. ~~All other participants will be followed for 96 weeks after randomization or assignment to the last step they enter.~~

For participants who did not receive ET while on study, the duration of follow-up will be as follows:

- **Participants who are randomized ONLY to Step 1 and who do not enter Step 2 or 3 will be followed for 96 weeks from Step 1 entry;**
- **Participants who are randomized to Step 2 and/or 3 will be followed for 48 weeks after entry into the last step that they enter.**

17. Section 11.3, Clinical Site Monitoring and Record Availability

The second paragraph of this section has been revised to read:

The site investigator will make study documents (e.g., consent forms, drug distribution forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the NIAID, the OHRP, **other local, US, and international regulatory entities** ~~government agencies~~, and the ~~pharmaceutical industry~~ supporters or designee for confirmation of the study data.

18. Section 12.2, Participant Confidentiality

This section has been revised to read:

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by **the ACTG, IRB/EC, the NIAID, the OHRP, other local, US, or international regulatory entities as part of their duties,** ~~government agencies~~, or the ~~pharmaceutical industry~~ supporters or designee.

19. Appendix VI, Sample Informed Consent, Title

The protocol title in Appendix VI has been revised to read:

A-Randomized Comparison of Three Regimens of Chemotherapy with Compatible Antiretroviral Therapy for Treatment of Advanced AIDS-KS in Resource-Limited Settings

20. Appendix VI, Sample Informed Consent, WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

The first paragraph, second sentence, of this section has been revised to read:

If you join this study and ~~do NOT take ET while you are on the study~~, you will be in the study for **about up to two and a half years after you start your last step on the study.**

21. Appendix VI, Sample Informed Consent, WHAT ABOUT CONFIDENTIALITY?

The second paragraph of this section has been revised to read:

Your records may be reviewed by the US Food and Drug Administration (FDA), the ACTG, the US Office for Human Research Protections (OHRP), **or other local, US, and international regulatory entities** as part of their duties (insert name of site) institutional review board (IRB) or Ethics Committee (a committee that protects the rights and safety of participants in research), **National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study**, and their designees.

22. Protocol Signature Page

Per a new regulatory requirement by the Division of AIDS (DAIDS), a Protocol Signature Page (PSP) is appended for submission to DAIDS Protocol Registration System (DPRS) as part of the LOA registration packet.

The information above will be incorporated into the next protocol version as necessary if the protocol is amended.

Randomized Comparison of Three Regimens of Chemotherapy with Compatible Antiretroviral
Therapy for Treatment of Advanced AIDS-KS in Resource-Limited Settings

SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

A5263/AMC066

**Randomized Comparison of Three Regimens of Chemotherapy with Compatible
Antiretroviral Therapy for Treatment of Advanced AIDS-KS in Resource-Limited Settings**

**A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)
and
AIDS Malignancy Consortium (AMC)**

**Sponsored by:
National Institute of Allergy and Infectious Diseases (NIAID)
National Cancer Institute (NCI)
National Institute of Dental and Craniofacial Research (NIDCR)**

**Pharmaceutical Support Provided by:
Bristol-Myers Squibb, Inc.
Gilead Sciences, Inc.
Merck & Co., Inc.**

Non-IND study

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**FINAL Version 3.0
December 7, 2016**



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STUDY MANAGEMENT

All questions concerning this protocol should be sent via e-mail to the A5263/AMC066 Clinical Management Committee (CMC) at actg.cmca5263@fstrf.org. In the e-mail include "A5263" in the participant line and the name of your site in the message area. The appropriate member of the CMC will respond via e-mail with a "cc" to the CMC. A response should generally be received within 48 hours (Monday-Friday) excluding major US holidays.

The CMC consists of the protocol co-chairs, statisticians, DAIDS clinical representative and pharmacist, data manager, clinical trials specialists, and other protocol team members identified by the A5263/AMC066 team leadership.

Protocol E-mail Group

Sites registering to this study must contact the **User** Support Group at the Data Management Center (DMC) to have the relevant personnel at the site added to the actg.protA5263 e-mail group. Include the protocol number in the e-mail subject line.

- Send an e-mail message to actg.user.support@fstrf.org

Clinical Management

For questions concerning entry criteria, toxicity management, concomitant medications, and co-enrollment, contact the CMC.

- Send an e-mail message to actg.cmca5263@fstrf.org
- Include the protocol number, patient identification number (PID), and a brief relevant history

Sites must contact the CMC to request permission to make changes in antiretroviral drug regimens and chemotherapy regimens.

Sites are encouraged to contact the CMC with eligibility or any other questions.

Independent Endpoint Review Committee (IERC)

For questions concerning disease progression and moving a participant to a successive study step, sites must contact the IERC.

- Send an e-mail to ACTG.IERCA526364@fstrf.org
- Please refer to the A5263/AMC066 Manual of Operations for detailed instructions

Laboratory

For questions specifically related to virologic or pharmacologic laboratory tests, contact the protocol virologist or pharmacologists.

- Send an e-mail message to actg.teamA5263@fstrf.org (ATTN: Richard Ambinder **and Dirk Dittmer**, virologists; Courtney Fletcher and Michelle Rudek, pharmacologists)

Data Management

For nonclinical questions about transfers, inclusion/exclusion criteria, case report forms (CRF), the CRF schedule of events, randomization/registration, delinquencies, and other data management issues, contact the Data Manager.

- For transfers, reference the **Study Participant Transfer** SOP 119, and contact **Stephanie Caruso** directly

STUDY MANAGEMENT (Cont'd)

- For other questions, send an e-mail message to actg.teamA5263@fstf.org (ATTN: **Stephanie Caruso**)
- Include the protocol number, PID, and a detailed question

Randomization

For randomization questions or problems and study identification number (SID) lists.

- Send an e-mail message to actg.support@fstf.org

Computer and Screen Problems

Contact the SDAC/DMC programmers.

- Send an e-mail message to rando.support@fstf.org

Protocol Document Questions

- For questions concerning the protocol document, contact the Clinical Trials Specialists.
- Send an e-mail message to actg.teamA5263@fstf.org (ATTN: Lara Hosey and Jennifer Rothenberg)

Copies of the Protocol

To request a hard copy of the protocol, send a message to ACTGOpsCenter@s-3.com (ATTN: Diane Delgado) via e-mail. Electronic copies can be downloaded from the ACTG website.

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Study Drug

For questions or problems regarding study drug, dose, supplies, records, and returns, call Katherine Shin, Protocol Pharmacist, at 240-627-3047.

Study Drug Orders

Call the Clinical Research Products Management Center at 301-294-0741.

IND (Investigational New Drug) Number or Questions

Contact the DAIDS RSC at Regulatory@tech-res.com or call 301-897-1706.

Expedited Adverse Event (EAE) Reporting/Questions

Contact DAIDS through the RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 301-897-1709; or fax 1-800-275-7619 or 301-897-1710.

Telephone Calls

Sites are responsible for documenting any telephone calls made to A5263/AMC066 team members.

- Send an e-mail to actg.teamA5263@fstrf.org

Protocol-Specific Web Page

Additional information about management of the protocol can be found on the protocol-specific web page (PSWP).

GLOSSARY OF TERMS

ABC	abacavir
ABV	doxorubicin (adriamycin)/bleomycin/vincristine
AE	adverse event
AIDS-KS	AIDS-related Kaposi's sarcoma
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
BID	twice daily
BPNS	brief peripheral neuropathy screen
BV	bleomycin and vincristine
CCDSMB	DAIDS Co-infections and Complications Data Safety Monitoring Board
CI	confidence interval
CM	cryptococcal meningitis
CMC	Clinical Management Committee
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CR	complete response
CRF	case report form
CRPMC	Clinical Research Products Management Center
CT scan	computed axial tomography
CXR	chest X-ray
ddl	didanosine
d4T	stavudine
DAIDS	Division of AIDS
DMC	Data Management Center
EAE	expedited adverse event
E/CIA	enzyme/chemiluminescence
EFV	efavirenz
ET	etoposide
FDA	Food and Drug Administration
FDC	fixed dose combination
FTC	emtricitabine
G-CSF	granulocyte-colony-stimulating factor
HAART	highly active antiretroviral therapy
HBM	human biological materials
HBsAg	hepatitis B surface antigen

GLOSSARY OF TERMS (Cont'd)

HBV	hepatitis B virus
HHV-8	human herpesvirus 8
ICF	informed consent form
IERC	Independent Endpoint Review Committee
IRB	Institutional Review Board
IQA	Immunology Quality Assurance
ITT	intention to treat
IV	intravenous
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpesvirus
KS-IRIS	Kaposi's sarcoma-associated immune reconstitution inflammatory syndrome
LDMS	Laboratory Data Management System
3TC	lamivudine
LFT	liver function test
LPC	lab processing chart
LPV	lopinavir
MOPS	Manual of Operations
MTCT	mother-to-child transmission
NIAID	National Institute of Allergy and Infectious Diseases
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
OHRP	Office for Human Research Protections
PBMC	peripheral blood mononuclear cell
PCP	pneumocystis jiroveci pneumonia
PI/r	protease inhibitor/ritonavir
PD	progressive disease
PFS	progression-free survival
PID	Patient Identification Number
PIP	predicted interval plots
PK	pharmacokinetics
PLD	pegylated liposomal doxorubicin
PN	peripheral neuropathy
PR	partial response
PSWP	protocol-specific web page
PTX	paclitaxel
QD	once daily
RSC	Regulatory Support Center
RLS	resource-limited settings
RTV	ritonavir
SDAC	Statistical and Data Analysis Center

GLOSSARY OF TERMS (Cont'd)

SID	study identification number
SIP	site implementation plan
SOE	schedule of events
SPN	symptomatic peripheral neuropathy
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TMA	tissue microarray
ULN	upper limit of normal
VQA	Virology Quality Assurance
WBC	white blood cell
ZDV	zidovudine

SCHEMA
A5263/AMC066

A Randomized Comparison of Three Regimens of Chemotherapy with Compatible Antiretroviral Therapy for Treatment of Advanced AIDS-KS in Resource-Limited Settings

- DESIGN:** This is a prospective, randomized, active-controlled, **two-arm** clinical trial.
- DURATION:** **Participants who received etoposide (ET) while on study will be followed for 144 weeks after beginning the last cycle of ET. All other participants** will be followed for **96 weeks** after randomization or assignment to the last step they enter.
- SAMPLE SIZE:** **446** participants ≥ 18 years of age (**386** randomized to Arm 1B or Arm 1C, **plus 60** who were previously randomized to Arm 1A in an earlier version of the protocol)
- POPULATION:** HIV-infected men and women with the following characteristics:
- Biopsy diagnostic of KS
 - Naïve to ART (as defined in section 4.2.7), chemotherapy, and radiation therapy
 - KS stage T1, (see section 4.1.3)
 - Persons with chronic, acute, or recurrent infections that are serious, in the opinion of the site investigator, must have completed at least 14 consecutive days of appropriate anti-infective treatment prior to study entry and be clinically stable
- STRATIFICATION:** Randomization will be stratified by CD4+ lymphocyte cell count (<100 or ≥ 100 cells/mm³) and by country
- REGIMEN:** **Step 1:**
- Arm 1A:** ET 50 mg plus coformulated efavirenz, tenofovir, and emtricitabine (EFV/FTC/TDF) twice a day.
- At an interim review in March 2016, the DAIDS Co-infections and Complications Data Safety Monitoring Board (CCDSMB) found that the ET plus ART arm was less effective than the paclitaxel (PTX) plus ART arm. Per the CCDSMB recommendation, enrollment into this arm and all initiation of ET in subsequent steps were discontinued in March 2016.**
- Arm 1B:** Bleomycin 15 units/m² IV (intravenous) plus vincristine 2mg IV plus coformulated EFV/FTC/TDF every 3 weeks. Treatment with BV may continue for a maximum of six cycles, or until toxicity requiring discontinuation of study chemotherapy, or until the site investigator and the CMC have determined that alternative therapy is required, whichever occurs first.
- Arm 1C:** PTX 100 mg/m² IV plus coformulated EFV/FTC/TDF every 3 weeks. Treatment with PTX will continue for a maximum of six cycles, or until toxicity

SCHEMA (Cont'd)

requiring discontinuation of study chemotherapy, or until the site investigator and the CMC **have** determined that alternative therapy is required, whichever occurs first.

Step 2:

A second course of up to six cycles of the same chemotherapy utilized in Step 1 plus coformulated EFV/FTC/TDF. **Participants who completed one course of ET will not receive a second course of ET. These participants will be entered into Step 3.**

Step 3:

The remaining study-provided chemotherapy regimen (BV or PTX) plus coformulated EFV/FTC/TDF. **For those who received ET in Step 1 and/or Step 2, BV or PTX will be randomly assigned.**

Step 4:

Please note that Step 4 applies only to those who received ET in Step 1, Step 2, or Step 3. The remaining study-provided chemotherapy regimen (BV or PTX) plus coformulated EFV/FTC/TDF.

***Step 1:**

Arm 1B: BV + EFV/FTC/TDF
Arm 1C: PTX + EFV/FTC/TDF

progression at any time during Step
progression **fewer than** 12 weeks
herapy dose in Step 1 **in participants**
RC-confirmed CR or PR OR
progression following Step 1
out any prior response OR

- se eligible for Step 2 who, in the
tigator and with concurrence of
y to benefit from another course
therapy received in Step 1

A second course of up to six cycles of the
same chemotherapy utilized in Step 1
+
EFV/FTC/TDF

- **Step 3:**
Remaining study-provided chemotherapy regimen
+
EFV/FTC/TDF

- *Participants currently receiving ET in Step 1 or Step 2 may continue and complete ET or discontinue ET and enter Step 3 in discussion with the local investigator and in consultation with the CMC**

Step 4:
Remaining study-provided
chemotherapy
+
EFV/FTC/TDF

**Alternative care available
locally outside of the
study**

1.0 STUDY OBJECTIVES

1.1 Primary Objective

To compare the clinical efficacy of two regimens, **etoposide (ET)** plus ART and **bleomycin plus vincristine (BV)** plus ART, to **paclitaxel (PTX)** plus ART for initial treatment of advanced stage **AIDS-related Kaposi's sarcoma (AIDS-KS)**.

1.2 Secondary Objectives

- 1.2.1 Compare **Kaposi's sarcoma (KS)** tumor response in persons randomized to ET plus ART, BV plus ART, and PTX plus ART.
- 1.2.2 Compare measures of quality of life in persons randomized to ET plus ART, BV plus ART, and PTX plus ART.
- 1.2.3 Compare the safety and toxicity in persons randomized to ET plus ART, BV plus ART, and PTX plus ART.
- 1.2.4 Compare suppression of plasma HIV-1 RNA and changes in CD4+ lymphocyte cell count in persons randomized to ET plus ART, BV plus ART, and PTX plus ART.
- 1.2.5 Compare adherence to ART in persons randomized to ET plus ART, BV plus ART, and PTX plus ART.
- 1.2.6 Compare the incidence of peripheral neuropathy (PN) and symptomatic peripheral neuropathy (SPN) in persons randomized to ET plus ART, BV plus ART, and PTX plus ART.
- 1.2.7 **Evaluate** clinical efficacy of the **remaining regimen** after failure of **the** initial regimen.
- 1.2.8 Evaluate the relationship between response of KS to therapy and development of KS-associated immune reconstitution inflammatory syndrome (KS-IRIS) with:
 - 1.2.8.1 Baseline immunohistochemical markers of viral and cellular gene expression in KS tumors.
 - 1.2.8.2 RNA levels for **Kaposi's sarcoma herpesvirus (KSHV)** genes in tumor biopsies at baseline and during therapy.
 - 1.2.8.3 Suppression of KSHV viral load.
 - 1.2.8.4 Cellular and humoral markers of immune function and immune activation.

- 1.2.9 Investigate the relationship between plasma and peripheral blood mononuclear cell (PBMC) KSHV viral load.
- 1.2.10 Encourage donation of excess biopsy materials to the AIDS and Cancer Specimen Resource.
- 1.2.11 To assess the risk of secondary leukemia and myelodysplasia after **ET**.

2.0 INTRODUCTION

2.1 Background

AIDS-KS occurs in persons who are coinfectd with HIV-1 and human herpesvirus 8 (HHV-8 or KSHV). The availability of potent ART has coincided with a substantial decrease in AIDS-KS incidence in the United States and Europe since the mid-1990s. Nonetheless, AIDS-KS remains the most commonly diagnosed AIDS-associated malignancy in developed countries [1], and may occur even among people who have apparently effective HIV control [2,3]. In areas of the world where access to ART and chemotherapy is limited, and where rates of HIV and KSHV coinfection are much higher than in developed countries [4-7], AIDS-KS is an even more significant contributor to morbidity and mortality in HIV-1 infected persons.

2.1.1 Treatment of AIDS-KS with ART

In developed countries, standard treatment for persons who are ART-naïve consists of three-drug combinations of two nucleoside reverse transcriptase inhibitors (NRTIs) with either an HIV-1 protease inhibitor with ritonavir boosting (PI/r) or a non-NNRTI. These regimens provide effective inhibition of HIV-1 replication that results in functional immune reconstitution, decreased risk of AIDS-related events, and improved survival [8-12].

A dramatic decrease in the incidence of KS in HIV-1-infected populations in developed countries has coincided with the widespread use of antiretroviral (ARV) agents to manage HIV-1 infection [12,13]. In many cases the use of highly active antiretroviral therapy (HAART) alone results in regression of KS lesions. KS improvement or complete resolution of lesions has been reported in up to 55-60% of patients [14-16] even though ARV agents do not affect KSHV replication in cultured cell lines. Pilot studies have demonstrated that treatment of AIDS-KS with ART is safe and provides effective suppression of HIV-1 and increased lymphocyte cell counts in South Africa [17] and is associated with improved retention in care in Malawi [18] and improved survival in Zimbabwe [19] compared to chemotherapy alone. Although some data suggest that ART alone is often adequate treatment for newly diagnosed limited-stage AIDS-KS, response to ART alone does not invariably occur or is sometimes incomplete. Given that ART alone often improves or stabilizes AIDS-KS disease, it is possible

that combining ART with chemotherapy might provide improved clinical responses. Data from prospective randomized studies of chemotherapy in combination with ART are limited, and the optimal approach to treatment of more advanced-stage (T1) AIDS-KS in the ART era, particularly in resource-limited settings, has not been defined.

2.1.1.1 Emtricitabine and Tenofovir Disoproxil Fumarate (**Truvada**, FTC/TDF) Fixed Dose Combination (FDC) Tablet

Truvada (Gilead Sciences), a product containing FTC 200 mg and TDF 300 mg in an FDC tablet formulation was approved by the United States Food and Drug Administration (US FDA) on August 2, 2004.

Study GS-US-104-172 was a phase I, 28-day, randomized, four-way crossover, pharmacokinetic (PK) study in healthy volunteers designed to evaluate the bioequivalence of the FTC/TDF combination tablet compared with the FTC capsule and TDF tablet administered concurrently and also the effect of food (high-fat meal and light meal) on PK [20]. The results demonstrated bioequivalence between the FTC/TDF combination tablet and the FTC capsule and TDF tablet formulations when administered separately. Administration of the FTC/TDF combination tablet with either a high-fat meal or light meal increased TDF exposure by approximately 30% compared with fasted-state administration. Clinical experience with TDF indicates that the effect of food on TDF exposure is not of clinical relevance. FTC and TDF, either administered as an FDC tablet (containing FTC 200-mg/TDF 300-mg) or co-administered as FTC 200 mg capsule and TDF 300-mg tablet separately, were well tolerated.

Several studies have assessed the safety and efficacy of FTC with TDF, although none using FDC. Study M02-418 was a phase III, randomized, open-label, multicenter study designed to compare lopinavir (LPV) 800 mg/ritonavir (RTV) 200 mg QD (once daily) versus LPV 400 mg/RTV 100 mg BID (twice daily) with the background regimen of FTC 200 mg QD and TDF 300 mg QD in ART-naïve patients with HIV-1 RNA >1000 copies/mL [21-23]. A total of 190 patients between the ages of 19-75 years were enrolled; 115 to the QD arm and 75 to the BID arm. At week 48, based on the intention to treat (ITT) (NC=F) analysis, 70% of participants in the QD regimen demonstrated HIV-1 RNA <50 copies/mL compared with 64% of those in the BID group (95% CI: -7%; 20%). Gastrointestinal adverse events (AEs) were the most common cause for discontinuation. Overall, the most common AEs (>3%) reported were diarrhea, nausea, and vomiting, with diarrhea being reported significantly higher in the QD group (16% versus 5%; p=0.04). The most common Grade 3/4 laboratory abnormalities (>3%) reported were increased alanine aminotransferase (ALT) (>5×upper limit of normal [ULN]), aspartate aminotransferase (AST) (>5×ULN), triglyceride (>750

mg/dL), and amylase ($>2\times$ ULN) levels; no significant differences between the two groups were observed [23].

Study 934 is a phase III, randomized, open-label, noninferiority, multicenter study designed to compare a regimen of TDF 300 mg + FTC 200 mg + EFV (efavirenz) QD with a regimen of ZDV (zidovudine) 300 mg/3TC (lamivudine) 150 mg BID (as FDC Combivir) + EFV QD in ARV-naïve, HIV-1-infected participants [24]. The 48-week data demonstrated that using the time to loss of virologic response as the primary analysis (where missing, switch, or early termination is counted as a failure), the proportion of participants with plasma HIV-1 RNA levels <400 copies/mL in an ITT population ($n=487$) was 84% in the TDF+FTC group compared with 73% in the ZDV/3TC group ($p=0.002$). The proportion of participants with plasma HIV-1 RNA levels <50 copies/mL was 80% in the TDF+FTC group versus 70% in the ZDV/3TC group ($p=0.020$). Significant differences were also seen between the TDF+FTC and the ZDV/3TC groups in the proportion of participants with increases in CD4+ cell counts (190 and 158 cells/mm³, respectively; $p=0.002$).

Safety analysis, based on 511 participants who received any study medication, showed that discontinuation due to AEs occurred more frequently in the ZDV/3TC group (9%) than in the TDF+FTC group (4%) ($p=0.02$). The most common AE resulting in discontinuation related to study drug for the ZDV/3TC group was anemia (14/254) and NNRTI-associated rash (2/257) for the TDF+FTC group. Renal safety was similar in the two groups, and no participant discontinued study medication because of renal events. A significantly ($p<0.001$) greater percentage of participants in the TDF+FTC arm had a lower mean increase from baseline in fasting total cholesterol levels (21 mg/dL) compared with participants in the ZDV/3TC arm (35 mg/dL). At week 48, total limb fat was significantly less in a subset of participants receiving ZDV/3TC (mean of 6.9 kg or 15.2 pounds; $n=49$) compared with a subset of participants receiving TDF+FTC (mean 8.9 kg or 19.6 pounds; $n=51$; $p=0.03$). All participants with confirmed >400 copies/mL of HIV-1 RNA at week 48 or early discontinuation were analyzed for genotypic resistance. Genotype data were limited to 23 participants on ZDV/3TC and 12 participants on TDF+FTC and showed mostly M184V/I (3% in ZDV/3TC participants versus 1% in TDF+FTC participants) and/or EFV-resistance mutations (7% in ZDV/3TC versus 4% in TDF+FTC participants), with no participants developing the K65R mutation.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including FTC, TDF, and other ART.

FTC/TDF is designated as US FDA use-in-pregnancy Category B. More information concerning FTC/TDF coformulation is available in the most recent Truvada package insert.

2.1.1.2 Efavirenz (Stocrin, EFV)

EFV is a once daily NNRTI that has been shown to be effective in the treatment of HIV disease [25].

The most notable side effects associated with EFV are central nervous system (CNS) symptoms and rash. Fifty-three percent of those receiving EFV reported CNS symptoms. These symptoms included, but were not limited to, dizziness, impaired concentration, somnolence, abnormal dreams, and insomnia. Symptoms usually begin during the first or second day of therapy and generally resolve after the first 2 to 4 weeks of therapy. Symptoms may also be less noticeable if EFV is taken at bedtime. Potential for additive symptoms may occur if used concomitantly with alcohol or psychoactive drugs. Nervous system symptoms were severe in 2.0% of patients receiving EFV 600 mg QD and in 1.3% of patients receiving control regimens; and, 2.1% of EFV-treated patients discontinued therapy because of nervous system symptoms.

In multi-study comparisons of EFV-treated versus controls, severe acute depression (1.6% versus 0.6%) and suicidal ideation (0.6% versus 0.3%) were reported. Participants with a history of psychiatric disorder are at greater risk. There have been occasional post-marketing reports of delusions and aberrant behavior, predominantly in those with a history of mental illness or substance abuse. Participants who experience psychiatric symptoms should contact their doctor immediately to assess the possibility that the symptoms may be related to EFV.

Among approximately 2200 treated individuals in studies and expanded access programs, the incidence of Grade 4 rash (e.g., erythema multiforme and Stevens-Johnson syndrome) was 0.14%. The median time to onset of rash in adults was 11 days, and the median duration was 16 days. EFV should be discontinued in persons developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash.

Other side effects associated with EFV include upset stomach, diarrhea, anorexia, headache, tiredness, pancreatitis, elevated cholesterol (including high-density lipoprotein), elevated triglycerides, and elevated transaminase.

Teratogenicity/Developmental Toxicity

The US FDA use-in-pregnancy category for EFV has been changed from Category C (Risk of Fetal Harm Cannot Be Ruled Out) to Category D (Positive Evidence of Fetal Risk). This change is a result of four retrospective reports of neural tube defects in infants born to women with first trimester exposure to EFV, including three cases of meningocele and one of Dandy Walker syndrome. As EFV may cause fetal harm when administered during the first trimester to a pregnant woman, pregnancy should be avoided in women receiving EFV. Women of reproductive potential and women with bilateral tubal ligation should be counseled on the possible risks associated with pregnancy. Women should be instructed not to breastfeed while taking EFV. If a woman becomes pregnant while taking EFV during the first trimester of pregnancy, she should be apprised of the potential harm to the fetus.

Additional information regarding EFV is available in the most recent Stocrin package insert.

2.1.1.3 Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate FDC Tablet (Atripla, EFV/FTC/TDF)

Merck and Company has developed Atripla, a product containing EFV 600 mg, FTC 200 mg, and TDF 300 mg in a white color, FDC tablet for distribution outside of the **United States**.

Clinical study 934 supports the use of EFV/FTC/TDF in ART-naïve HIV-1-infected patients. Additional data supporting the use of EFV/FTC/TDF is found in the package insert for tenofovir (Viread). In ART-experienced patients, the use of EFV/FTC/TDF may be considered for patients with HIV-1 strains that are expected to be susceptible to the components of Atripla as assessed by treatment history or by genotypic or phenotypic testing.

2.1.2 Treatment of AIDS-KS with Chemotherapy

Although **HAART** alone may lead to regression of limited-stage (T0) AIDS-KS [26], the morbidity and mortality associated with advanced or rapidly progressive AIDS-KS usually mandates concomitant treatment with ART and chemotherapy. While a number of single chemotherapeutic agents and drug combinations may induce regression of AIDS-KS, the most effective regimen(s) to use in combination with ART have not been well defined, because many of the commonly-used regimens were tested prior to the introduction of highly active ART. In addition, relatively few studies have compared the efficacy of different chemotherapeutic regimens in randomized, phase III trials.

In the 1980s, a number of drugs previously approved for other cancer indications, including doxorubicin, bleomycin, ET, vincristine, and vinblastine, were shown to have single-agent activity against AIDS-KS. Intravenously administered ET was one of the first agents shown to have activity against AIDS-KS in the **United States** [27], and later studies conducted by the ACTG documented the activity of oral ET, yielding identical objective response rates of 36% using two different ET dosing regimens [28,29]. In addition, oral ET was shown to be superior to supportive care with respect to tumor response, and was superior to a combination of actinomycin D, bleomycin, and vincristine with respect to toxicity and quality of life in a randomized trial conducted in Zimbabwe prior to the availability of ART [30]. In the latter study, although combination chemotherapy was superior to ET with respect to tumor response, survival in both arms was similar.

Although single-agent ET has activity against AIDS-KS, combination chemotherapy regimens were more commonly used to treat AIDS-KS in the 1980s and early 1990s. Among the more widely used regimens were alternating weekly doses of vincristine and vinblastine [31], and combinations of bleomycin (B) and vincristine (V), with or without doxorubicin (A), so-called ABV or BV regimens. Estimates of the response rates induced by these regimens have varied from study to study, and it is not clear whether these differences reflect different patient characteristics, different response definitions and assessment methods, or both. For example, BV reportedly induced major (defined as either complete response, i.e., complete disappearance of all lesions, or partial response, i.e., $\geq 50\%$ tumor size reduction) objective responses in 57% of patients in a study by Gompels et al. [32], but in only 23% of patients in a large randomized comparison with pegylated liposomal doxorubicin (PLD) [33]. A review of several studies conducted at the University of Southern California (USC) [34] reported that BV and ABV induced major responses in 76-81% of patients. Other studies from USC and multicenter trials conducted by the ACTG reported major response rates as high as 88% for ABV [35-37]. However, two large, randomized, multicenter trials in which ABV was compared with liposomal daunomycin [38] or PLD [39] yielded response rates of only 28% and 25%, respectively, in the ABV arms.

Although the aforementioned drugs and drug combinations were widely used to treat AIDS-KS from the very early days of the AIDS epidemic in the US, until the mid-1990s no drugs (with the exception of recombinant interferon alfa which, by virtue of its high cost, side effect profile, inconsistent activity in advanced disease, and need for parenteral self-administration, is unsuited for use in resource-limited settings) had received the type of rigorous testing required for US FDA approval for an AIDS-KS indication. Then, in the mid- to late-1990s, three drugs – two newly-introduced liposomal anthracyclines, PLD (Doxil; Caelyx) and liposomal daunorubicin (DaunoXome), and an older, established drug, paclitaxel (PTX; Taxol), originally approved in 1992 for treatment of metastatic breast and ovarian cancers and available in generic form for **more than a decade** – received US FDA approval for treatment of advanced,

symptomatic AIDS-KS. Although PTX induced high objective response rates in AIDS-KS, including responses in patients who had previously been treated with liposomal anthracyclines [40-42], until recently PLD was the agent most commonly selected as first-line chemotherapy for advanced, symptomatic AIDS-KS in high-resource countries. The preference for PLD was based on its adverse event profile and acceptability to patients, in particular the infrequency of PLD-induced alopecia, despite substantially higher cost. In 2011, however, because of manufacturing problems at its only worldwide production facility, PLD became unavailable, and the timing of its future availability is uncertain. This has led to a re-examination of alternatives for treatment of AIDS-KS and a renewed interest in the role of PTX as first-line therapy for patients with advanced, potentially life-threatening KS.

PTX was approved by the US FDA in 1997 as second-line therapy for AIDS-KS on the basis of two phase II open-label studies each of which evaluated a different treatment regimen: 135 mg/m² as a 3-hour infusion every 3 weeks, and 100 mg/m² as a 3-hour infusion every 2 weeks [40,41,43]. Of 85 patients analyzed at the time of FDA review, 59 had received prior systemic therapy for KS, including anthracyclines in 64%, and 93% had T1 (poor risk) disease. A major objective response, as documented in 59% of patients (95% CI, 46-72%), and treatment was associated with clinical benefits that included improved pulmonary function in patients with pulmonary KS; improved ambulation, resolution of ulcers, and decreased analgesic requirements in patients with KS of the feet; and resolution of facial lesions and edema in patients with KS involving the face, extremities, and genitalia. The median time to response was 8.1 weeks and the median duration of response, measured from the first day of treatment, was 10.4 months (95% CI, 7.0-11.0 months) for patients who previously had received chemotherapy. The median time to progression was 6.2 months (95% CI, 4.6-8.7 months). Although both treatment regimens induced KS regression, the regimen of 100 mg/m² every 2 weeks was better tolerated than 135 mg/m² every 3 weeks, with substantially lower frequencies of severe neutropenia (35% versus 76%), febrile neutropenia (9% versus 55%), and opportunistic infections (54% versus 76%) among patients in the former group. Notably, only a minority of patients were receiving combination ART and 88% had a CD4+ count <200 cells/μL, reflective of the era in which these studies were conducted. Subsequent studies have confirmed the earlier findings. For example, Tulpule et al [41] reported the results in 107 previously treated patients, 85% of whom had received one or more prior anthracyclines including doxorubicin (49%), PLD (37%), and liposomal daunorubicin (46%) but had developed progressive KS or treatment intolerance. Complete or partial response was documented in 60 patients (56%) treated at a PTX dose of 100 mg/m² as a 3-hour infusion every 2 weeks, with a median response duration of 8.9 months. Similar findings were noted in a British study reported by Stebbing et al. [42] that used the same PTX dose and schedule. Amongst 17 patients whose KS had progressed within 6 months of receiving a liposomal anthracycline, 71% (95% CI, 60-81%) showed a major objective response.

Only one clinical trial has attempted to assess PTX's efficacy as first-line chemotherapy for advanced AIDS-KS and to compare its efficacy to that of PLD [44]. Although the study, a joint effort of the AIDS Malignancy Consortium (AMC) and the Eastern Cooperative Oncology Group (ECOG) that enrolled patients from 1998 to 2002, was terminated because of slow accrual, there were sufficient numbers of evaluable patients (n=73, 36 on PTX, 37 on PLD) to estimate antitumor efficacy and toxicity for each of the treatment arms. At baseline, 73% of the patients were receiving a combination ART regimen that included a protease inhibitor, an NNRTI, or both. Response and progression-free survival (PFS) were not significantly different in the PTX and PLD arms, but favored the PTX arm. Using an **ITT** analysis, the overall complete and partial response rate was 56% (95% CI, 39%-75%) for PTX and 46% (95% CI, 30%-62%) for PLD, and median PFS was 17.5 months (95% CI, 12.8-21) for PTX and 12.2 months (95% CI, 8.2-13.9) for PLD. PFS was marginally ($p=0.0582$) longer for patients receiving HAART (17 months) than for those not on HAART (9 months) at study entry.

The toxicity profiles of the agents to be used in this study, although overlapping in some cases, are distinct. Bleomycin treatment is often complicated by infusion-related fever and chills, generally requiring pre-medication with dexamethasone and diphenhydramine for control, and is also associated with cutaneous toxicities. With higher cumulative doses, pulmonary fibrosis may occur, and reduced but asymptomatic decreases in carbon monoxide diffusing capacity have been reported after lower doses. Vincristine frequently causes PN, and may cause jaw pain and constipation. Neither vincristine nor bleomycin is associated with significant hematologic toxicity. Serious or life-threatening toxicities associated with oral ET in AIDS-KS have mainly been confined to neutropenia, which occurred in about one-third of patients with chemotherapy-refractory disease who were entered into a trial of oral ET that used the same schedule proposed for the current study [29]. However, only 5 of 36 patients in this study were receiving a **HAART** regimen at the time of study enrollment. At the doses proposed for this study, the most commonly reported Grade 3 or 4 toxicity associated with PTX is neutropenia. Although PN is commonly reported with PTX, most cases are grade 1 or 2, and higher grades occur rarely. PTX preparations formulated with Cremophor EL (polyoxyethylated castor oil) may be associated with anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria. These reactions are rarely fatal. Premedication to prevent hypersensitivity reactions is required. The drugs are also quite different in their emetogenic potential: oral ET is considered to be associated with a moderate risk, PTX with a low risk, and bleomycin and vincristine with minimal risk of emesis. Oral ET carries no risk of local skin reactions; PTX has a low vesicant potential if extravasated; bleomycin is classified as an irritant, and vincristine has a high vesicant potential. Although these latter factors may not directly influence response to therapy, they can have a significant influence on treatment adherence and quality of life.

Because of their relatively low cost and widespread availability, either ABV or BV is the current standard of care for chemotherapy of AIDS-KS in many resource-limited settings. PTX is available in some low-resource settings, but has been used there primarily as second-line therapy in patients who have failed on ABV or BV [M. Borok, personal communication]. In some resource-limited settings, oral ET is also used for chemotherapy of AIDS-KS. Additionally, ET, unlike the other regimens discussed above, which require intravenous administration and can cause local tissue injury if extravasated, can be administered orally, which can provide significant logistic and cost advantages in resource-limited settings. Relatively little relevant data exist on which to base comparisons of the cost-effectiveness of the different available chemotherapeutic agents for AIDS-KS. Except for PLD, for which there is no generic form and cost is uniformly high (when available), all the other agents are available from multiple generic pharmaceutical manufacturers. Costs may vary significantly, however, from country to country, and it is not possible to compare costs across sites. In addition, the quality and potency of drugs obtained from unregulated generic manufacturers cannot be assured.

As noted above, the most effective regimens to use in combination with ART have not been well defined, because many of the drugs used to treat KS were tested prior to the introduction of **HAART**. There is, however, preliminary evidence that suggests that chemotherapy in combination with effective ART may provide benefit for individuals with AIDS-KS. Although 10-30% early mortality has been observed in AIDS-KS patients initiating ART in several African settings [45,46], in one pilot study treatment with combined chemotherapy and ART was associated with a decreased risk of early death for Zimbabweans with advanced AIDS-KS [47]. Data from randomized, controlled studies of systemic chemotherapy plus ART are limited [48]. In a randomized study of 28 advanced AIDS-KS cases in Spain, patients assigned to PLD plus ART had better tumor response rates than patients assigned to ART alone [49].

In a randomized comparison of ART alone versus ART plus a chemotherapy regimen of ABV in 33 South Africans, participants in the ART plus ABV arm had greater reductions in HHV-8/KSHV viral load and tended to have better tumor regression and less tumor progression [50].

2.1.3 Justification of A5263/AMC066 Regimens

As discussed above, there is relatively little available data on the relative performance of any of the chemotherapy regimens to be included in this study when used in combination with currently available ART, and there is no evidence-based standard of care for advanced KS in resource-limited settings. Each of the chemotherapy regimens we propose to test has induced responses in HIV-infected individuals with KS, but the populations studied and the response criteria used to evaluate efficacy were non-uniform. Thus, we consider that clinical equipoise exists between the three regimens, and that if one regimen in

this study is proven superior to the others, it will inform clinical practice worldwide.

2.1.3.1 Bleomycin plus Vincristine (BV)

The selection of BV, and its choice over ABV in this study was based on several considerations. First, the large, randomized, controlled trials of liposomal anthracyclines versus BV or ABV were all conducted pre-HAART. For example, in the randomized trial that compared PLD and BV reported by Stewart et al. [33], only half of the patients in each arm of the study were receiving any ART, and ART was confined to single or combination NRTIs. Little is known about the performance of “standard” non-liposomal chemotherapy in combination with ART regimens that conform to current standards of care and which have resulted in improved overall outcomes for people with AIDS-associated KS.

Second, in their 1998 paper, Stewart et al. [33] commented on the long-held perception that ABV offered a higher response rate, whereas BV offered a better toxicity profile. They noted that ABV and BV had never been directly compared in a clinical trial. Although reports had appeared in the literature citing response rates of 50% to 80% for these combinations, these studies did not use rigorous ACTG KS response criteria. In those studies that did use rigorous response criteria, such as the studies by Stewart et al. [33], Northfelt et al. [39] and Gill et al. [37], the response rates for both BV and ABV were much lower than had previously been reported in uncontrolled phase II studies, and were comparable to each other. Thus, in studies that used rigorous response criteria, there was no evidence that BV was inferior to ABV with respect to objective, strictly defined response rates. On the other hand, there was good evidence that BV had a superior toxicity profile compared to ABV, which was associated with a higher rate of hematologic toxicity and treatment delays for neutropenia and infection and also presents the risk of serious cardiotoxicity. In addition, as noted by Stewart et al. [33], BV was also associated with considerably less myelosuppression than liposomal doxorubicin, which may be particularly important in locales where hematopoietic growth factors like granulocyte-colony stimulating factor (G-CSF) are not available and where access to blood component transfusion is limited.

Finally, as part of the development of this study, we polled prospective sites about their standard of care for KS and whether they had concerns about using either regimen as part of this trial. Of the 14 sites responding to the survey, 4 listed BV as their standard of care, 6 listed ABV, 2 stated that they were able to administer liposomal anthracyclines but often used either BV or ABV because of their lower cost, and 2 stated that they did not routinely give KS treatment. Eleven sites had no concerns about using BV, one site was concerned about drug

availability after the trial, one site was concerned about interactions with ART, and one site felt that ABV was superior to BV. Ten sites had no concerns about using ABV, one site was concerned about drug availability after the trial, and three sites had other concerns that included toxicities of the regimen and issues with doxorubicin administration. Thus, there was no clear consensus “favorite,” but there were somewhat more concerns about ABV tolerance.

Thus, for all of the above reasons, the study team believes that inclusion of BV as a treatment arm in this study is justified and ethical, and that the results of this study will provide important information that will inform future treatment decisions for AIDS/KS in resource-limited settings.

Vincristine Interactions with Ritonavir

Vinca alkaloids, including vincristine and vinblastine, are primarily metabolized by CYP3A isoenzymes. Several case reports and small series have suggested that co-administration of Vinca alkaloids with the potent CYP3A inhibitor, ritonavir, may be associated with increased hematologic and neurotoxicity. In one small series of HIV-infected individuals with Hodgkin’s disease, severe neutropenia was observed more commonly among patients receiving ritonavir-boosted PI regimens than among those on non-boosted PIs or regimens that did not contain a PI [51], and two deaths from neutropenic sepsis were described. Severe, prolonged neutropenia (in one case associated with peripheral neuropathy and constipation) has also been reported in a patient with Hodgkin’s disease [52] and another with multicentric Castleman’s disease [53] who received vinblastine with ritonavir-containing ART. The patient with Castleman’s disease had multiple episodes when ritonavir and vinblastine were co-administered, but tolerated vinblastine well when not receiving ritonavir concomitantly. Another single case report described severe and prolonged paralytic ileus requiring parenteral feeding after co-administration of vincristine and lopinavir/ritonavir, an event that did not recur when ET replaced vincristine in the chemotherapy regimen. Although none of these studies included measurement of Vinca alkaloid pharmacokinetics, and further study is required, they suggest that alternatives to ritonavir should be used in HIV-infected patients with cancer who require Vinca alkaloid-containing chemotherapy regimens together with ART.

2.1.3.2 Etoposide (ET)

At an interim review in March 2016, the DAIDS Co-infections and Complications Data Safety Monitoring Board (CCDSMB) found that the ET plus ART arm was less effective than the PTX plus ART arm. Per the CCDSMB recommendation, enrollment into this arm and all initiation of ET in subsequent steps were discontinued in March 2016.

ET is a chemotherapeutic agent that has demonstrated efficacy for treatment of AIDS-KS. ET has potential advantages over the other regimens used in this study, particularly in resource-limited settings, including intermittent oral dosing without the need for the intensive clinical and pharmacy resources associated with the preparation and administration of intravenous chemotherapy, a favorable acute toxicity profile at low doses, and availability as a relatively inexpensive generic formulation. These advantages of ET need to be weighed against the long-term risk of myelodysplasia and acute leukemia associated with ET administration.

The Cancer Therapeutics Evaluation Program of the National Cancer Institute performed a combined analysis of 12 NCI-sponsored cooperative group protocols in which **ET** was administered [54]. They divided **ET** exposure into low ($<1.5 \text{ g/m}^2$ ET), moderate ($1.5\text{-}3.0 \text{ g/m}^2$) and high ($>3 \text{ g/m}^2$) exposure. They calculated the 6-year risk of secondary leukemia/myelodysplasia for the low, moderate, and higher cumulative dose groups as 3.3% (95% upper confidence bound of 5.9%), 0.7% (95% upper confidence bound of 1.6%), and 2.2%, (95% upper confidence bound of 4.6%), respectively. Overall there were 17 cases of leukemia with 5450 person-years of follow-up. These cases were not clustered near the time of chemotherapy and incidence rate appeared uniform over the 6 years of follow-up. All of these clinical trials gave ET in combination with other chemotherapy agents. The relationship of ET to leukemia in the absence of other chemotherapeutic agents is unknown.

Given the high risk of serious morbidity and mortality from advanced KS, the generally good safety and tolerance of oral ET, and the relatively low risk of these late complications, the use of ET in this study is justified.

2.1.3.3 Paclitaxel (PTX)

Only two chemotherapeutic agents, PLD and PTX, have received the rigorous evaluation required for US FDA approval for treatment of advanced AIDS-KS. Although long considered the standard initial treatment for advanced KS in developed countries, PLD is currently not available and its cost has prevented its widespread use in resource-limited settings. The data summarized above suggest that PTX, which, despite its availability as an affordable, generic product, is not generally used as first-line therapy in resource-limited settings, shows antitumor activity against KS that is similar to or better than that with PLD. At the doses used to treat AIDS-KS, PTX is generally well-tolerated, and can be considered an appropriate standard against which other treatments for advanced AIDS-KS in resource-limited settings should be compared. If this trial shows that therapy with currently available standard agents

(i.e., ET or BV) with ART are similar to those obtained with PTX with ART, this would favor the use of the less-expensive or better-tolerated regimen. On the other hand, if we find that PTX is clearly superior to the alternatives, this could provide important information that could influence policy concerning the availability and use of first-line chemotherapy in resource-limited settings.

Although in the previously cited clinical trials, PTX was administered over a 3-hour infusion, subsequent studies have shown that PTX can be safely administered over 1-hour, and many practitioners routinely use a 1-hour infusion for treatment of AIDS-KS and other malignancies [55]. In addition, 1-hour infusion times have been associated with less myelosuppression, presumably as a result of reduced exposure to unbound drug [56]. In addition to using the better-tolerated PTX dose of 100 mg/m² (as opposed to 135 mg/m²) to mitigate toxicity, we will also use an every 3 week administration schedule to permit sufficient recovery of blood counts under circumstances where hematopoietic growth factor support is not routinely available.

Based on the above considerations, we believe that the evaluation of PTX at the proposed dose, schedule, and infusion time in this study is justified.

PTX Interactions with Antiretroviral Therapy

PTX is metabolized in the liver predominantly by cytochromes P450 2C8 and 3A4 via saturable elimination **to less potent** metabolites, indicating that modest changes in dose or metabolizing enzyme activity could result in disproportionately large alterations in systemic exposure, potentially influencing toxicity and response. **In addition, PTX is a substrate for several drug transporters including ABCB1, ABCC1, ABCC2 and ABCG2.** Pharmacodynamic analyses have shown hematologic and non-hematologic toxicity to correlate better with parameters of **PTX** exposure (e.g., area under the plasma concentration-time curve (AUC) and duration of plasma concentrations exceeding 0.1 mmol/L) than with the administered dosage.

Although **PTX** has, for the most part, been well tolerated in combination with ART, rare reports of severe **PTX** toxicity have been attributed to concomitant **ART**, including protease inhibitors [57,58]. To address potential drug-drug interactions, a pilot study conducted jointly by the ECOG and AMC (AMC014/E1D95) evaluated the interactions between **PTX** and ART in patients with AIDS-KS [59]. Thirty-three patients received **PTX** as a 100 mg/m² IV infusion over 3 hours every 14 days, of whom 27 underwent PK studies. There was a trend for **PTX** maximum concentration (C_{max}) to be elevated in the 16 patients taking protease inhibitors (nelfinavir, indinavir, or multiple inhibitors) compared to the 11 patients not taking protease inhibitors (1.47±0.68 µM versus 1.01±0.34

μM ; $p=0.11$; Wilcoxon t-test). However, the **PTX** AUC_{inf} , which was evaluable in only 21 patients, was significantly higher in the 15 patients taking protease inhibitors compared to the 6 patients not taking protease inhibitors ($5.5 \pm 2.2 \mu\text{M hour}$ versus $2.9 \pm 0.7 \mu\text{M hour}$; $p=0.016$; Wilcoxon t-test). Yet, there was no difference in the duration spent at a **PTX** concentration $>0.05 \mu\text{M}$ (19.0 ($3.0\text{--}27.8$) hour versus 6.7 ($3.0\text{--}22.7$) hour; $p=0.97$). Patients with higher **PTX** exposure did not experience more significant granulocytopenia (C_{max} $p=0.96$; AUC_{inf} $p=0.83$; $\text{Time}>C_{0.5 \mu\text{M}}$ $p=0.09$; Wilcoxon t-test), and grade 3 or higher neurotoxicity occurred in only 5%.

EFV induces CYP3A4 and the transporter ABCC1 inhibits several drug transporters (ABCB1, ABCC1, ABCC2, and ABCG2). Based on the metabolic profiles of **PTX** and **EFV**, there is potential for interaction. However, there are no clinical data to support decreased efficacy or increased toxicity and currently no basis for changing the doses of either **PTX** or ART. The A5278 substudy will investigate these potential PK interactions.

2.2 Rationale

Most comparative clinical trials of different chemotherapy regimens for AIDS-KS were conducted prior to the availability of **HAART**, so scant data are available to guide the optimal use of chemotherapy in combination with ART. The need for such data is particularly acute in resource-limited settings where rates of HIV and KSHV co-infection are high, and where significant morbidity and mortality are associated with KS. In addition, despite evidence cited above that adjunctive chemotherapy might be beneficial for treatment of AIDS-KS, HIV-1 treatment programs often do not provide funding for chemotherapy in resource-limited countries. Thus, a well-designed clinical study to define the potential benefits of adjunctive chemotherapy in the treatment of advanced AIDS-KS in the era of **HAART** is needed to inform treatment guidelines. Such a study needs to take into account the ability of different treatments to induce KS regression, the impact of therapy on quality of life (including relief of KS-associated signs and symptoms, drug-related toxicities, and effects on HIV control), ease of administration of therapy (which may have an impact on adherence), and cost. Because there is no single chemotherapeutic agent that has proven superior to others in combination with ART, and because the availability of chemotherapeutic agents and the current standards for treatment of AIDS-KS differ in different resource-limited settings, a randomized comparison of **PTX** with either BV or ET is justified.

3.0 STUDY DESIGN

Step 1:

Participants will be randomized **1:1** to bleomycin and vincristine (BV) plus **antiretroviral therapy (ART)** or paclitaxel (PTX) plus (ART).

At an interim review in March 2016, the CCDSMB found that the ET plus ART arm was less effective than the PTX plus ART arm. Per the CCDSMB recommendation, enrollment into this arm and all initiation of ET in subsequent steps were discontinued in March 2016.

Step 2:

Participants who originally have an **Independent Endpoint Review Committee (IERC)**-confirmed (complete or partial [CR or PR]) Kaposi's sarcoma (KS) response to Step 1 chemotherapy and subsequent **IERC**-confirmed KS progression at least 12 weeks after the last dose of Step 1 chemotherapy, but prior to week 72, and who, in the opinion of the investigator, could potentially benefit from another course of the same chemotherapy, may be provided a second course of up to six cycles of the same chemotherapy utilized in Step 1.

Participants who completed one course of ET will not receive a second course of ET. These participants will be entered into Step 3.

Step 3:

Participants will move to Step 3 when (1) there is IERC-confirmed KS progression at any time during Step 1 chemotherapy; or (2) there is IERC-confirmed KS progression **fewer than** 12 weeks after the last chemotherapy dose in Step 1 in participants who have had an **IERC**-confirmed **CR or PR**; or (3) there is IERC-confirmed KS progression following Step 1 chemotherapy, without any prior response; or (4) there is IERC-confirmed KS progression in Step 2; or (5) **with concurrence of the CMC**, there is dose-limiting toxicity after receiving **fewer than** four cycles of chemotherapy in Step 1 or Step 2, in the absence of a CR or PR. Participants otherwise eligible for Step 2 who, in the opinion of the investigator **and with concurrence of the CMC**, are unlikely to benefit from another course of the same chemotherapy received in Step 1 will also be eligible for randomization in Step 3.

Participants must enter Step 3 within the 72 weeks following Step 1 randomization.

Participants will receive the chemotherapy not utilized in Step 1 (BV recipients will receive PTX; PTX recipients will receive BV).

If participants completed ET in Step 1 and/or Step 2, then the choice of BV or PTX will be randomly assigned (1:1).

Participants currently receiving ET in Step 1 or Step 2 may continue and complete ET or discontinue ET and enter Step 3 in discussion with the local investigator

and in consultation with the CMC. These participants will be randomized (1:1) to receive BV or PTX.

Step 4:

Please note that Step 4 applies only to those who received ET in Step 1, Step 2, or Step 3.

If there is IERC-confirmed KS progression in Step 3 or, with concurrence of the CMC, if there is dose-limiting toxicity after receiving fewer than four cycles of chemotherapy in Step 3, in the absence of a CR or PR, participants may enter Step 4 or be offered alternative care available locally outside of the study, whichever the investigator deems most appropriate. If an investigator offers locally-available alternative care, the participants will be followed according to their original Step 3 schedule.

Participants must enter Step 4 within 72 weeks following Step 1 randomization.

Participants will be assigned to the remaining study-provided chemotherapy not given in Step 1, Step 2, or Step 3.

Participants who are currently receiving ET in Step 3 may continue ET or discontinue ET and start the remaining chemotherapy regimen in Step 4 in discussion with the local investigator and in consultation with the CMC.

If there is IERC-confirmed KS progression in Step 4, participants may be offered alternative care available locally, outside of the study. If an investigator offers locally available alternative care, the participants will be followed according to their original Step 4 schedule.

Participants who receive ET while on study will be followed for 144 weeks after beginning the last cycle of ET. All other participants will be followed for 96 weeks after randomization or assignment to the last step they enter.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria Step 1

- 4.1.1 HIV-1 infection, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen, plasma HIV-1 RNA viral load.**

NOTE: The term “licensed” refers to a U.S FDA-approved kit or for sites located in countries other than the United States, a kit that has been certified or licensed by an oversight body within that country and validated internally.

WHO (World Health Organization) and CDC (Centers for Disease Control and Prevention) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.

4.1.2 Biopsy diagnostic of KS at any time prior to study entry.

4.1.3 Current KS stage T1 using ACTG criteria [29].

KS stage T1 is KS with any of the following:

- symptomatic tumor-associated edema
- tumor ulceration
- extensive oral KS (other than flat KS confined to the hard palate)
- gastrointestinal KS
- KS in any other non-nodal visceral organ (e.g., lung)

4.1.4 A minimum of five indicator KS cutaneous marker lesions (**or if fewer than five marker lesions are available, the total surface area of the marker lesion(s) must be $\geq 700 \text{ mm}^2$**) plus an additional two lesions greater or equal to 4x4 mm that are accessible for punch biopsy.

Please refer to **the** A5263/AMC066 Manual of Operations (MOPS) located on the PSWP for instructions on determining cutaneous marker lesions.

4.1.5 CD4+ lymphocyte cell count obtained within 28 days prior to study entry at a DAIDS-approved laboratory.

4.1.6 The following laboratory values obtained within 14 days prior to study entry:

- Absolute neutrophil count (ANC) $\geq 1000 \text{ cells/mm}^3$
- Hemoglobin $\geq 8.0 \text{ g/dL}$
- Platelet count $\geq 100,000/\text{mm}^3$
- Estimated creatinine clearance of $\geq 60 \text{ mL/min}$ using the formula:
$$\text{CrCl} = \{[140 - \text{age (years)}] \times [\text{weight (kg)}]\} \div [72 \times \text{serum Cr (mg/dL)}]$$

(multiply the result x 0.85 for female participants)

NOTE: The Cockcroft-Gault calculation program can be found on DMC website (<http://www.fstrf.org/ACTG/index.html>).

- AST (SGOT), ALT (SGPT), and alkaline phosphatase $<5\times\text{ULN}$
- Total bilirubin of $<1.5\times\text{ULN}$

- 4.1.7 Female study **participants** of reproductive potential (defined as girls who have reached menarche, women who have not been post-menopausal for at least 24 consecutive months, i.e., who have had menses within the preceding 24 months, or women who have not undergone surgical sterilization, specifically hysterectomy and/or bilateral oophorectomy) must have a negative serum or urine pregnancy test with a sensitivity of 15–25 mIU/mL performed within **48** hours before initiating the protocol-specified medications.
- 4.1.8 All participants must agree not to participate in a conception process (active attempt to become pregnant or to impregnate, donate sperm, in vitro fertilization).
- 4.1.9 If participating in sexual activity that could lead to pregnancy, the study **participant** must agree that two reliable forms of contraceptives will be used simultaneously while receiving protocol-specified medications, and for 12 weeks after stopping the medications.

Male participants must agree to use condoms while receiving protocol-specified medications and for 12 weeks after stopping the medications. Documentation of the second form of contraception, used by the female partner, is by report of the study participant.

Study **participants** who are not of reproductive potential (women who have been post-menopausal for at least 24 consecutive months or have undergone hysterectomy and/or bilateral oophorectomy or men who have documented azoospermia) are eligible without the use of contraceptives. Acceptable documentation of sterilization and menopause is specified in Appendix I **and includes physician report.**

- 4.1.10 Men and women age ≥ 18 years.
- 4.1.11 Ability to swallow oral medications and adequate venous access.
- 4.1.12 Karnofsky performance status ≥ 60 within 28 days prior to entry.
- 4.1.13 Ability and willingness of participant or legal guardian/representative to provide informed consent.
- 4.2 Exclusion Criteria Step 1
- 4.2.1 Current chronic, acute, or recurrent infections that are serious, in the opinion of the site investigator, for which the participant has not completed at least 14 days of therapy prior to study entry and/or is not clinically stable.

- 4.2.2 Serious illness requiring systemic treatment and/or hospitalization within 14 days prior to entry.
- 4.2.3 Current or history of known pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), emphysema, bronchiectasis, or diffuse or significant local radiographic interstitial infiltrates on chest x-ray (CXR) or computed axial tomography (**CT**) scan, that, in the opinion of the investigator, would exclude bleomycin use.

NOTE: **Participants** with an abnormal CXR or CT scan (which may indicate pulmonary KS) should undergo screening evaluations **to rule out an infectious cause, per standard of care. If available, other diagnostic procedures such as bronchoscopy should be considered to confirm the presence or absence of pulmonary KS and/or an infectious agent. These procedures should be completed outside the study.** These participants should be excluded if, in the opinion of the site investigator, use of bleomycin would be detrimental.

- 4.2.4 Oxygen saturation less than 90% and/or exercise desaturation greater than 4% within 14 days prior to study enrollment.

NOTE: Exercise is defined as any activity that will increase a participant's resting heart rate by at least 20 beats/minute.

- 4.2.5 Grade ≥ 3 peripheral neuropathy (PN).

NOTE: Severity of PN will be determined by the symptom severity scores from the Brief Peripheral Neuropathy Screen (BPNS), discussed in section 6.3.20.

- 4.2.6 Breastfeeding.
- 4.2.7 Receipt of ART for more than **42** days immediately prior to entry. ART is allowed within the **42**-day window prior to study entry.

NOTE: The use of single-dose nevirapine (NVP) or zidovudine (ZDV) for any period of time during pregnancy to prevent mother to child transmission (MTCT) of HIV is allowed.

NOTE: Successful post-exposure prophylaxis is allowed. Unsuccessful post-exposure prophylaxis is not allowed.

- 4.2.8 Prior or current systemic or locally administered chemotherapy.
- 4.2.9 Prior or current radiation therapy.
- 4.2.10 Prior or current immunotherapy, e.g., interferon alfa.

4.2.11 Corticosteroid use at doses above those given as replacement therapy for adrenal insufficiency within the last 30 days prior to study entry. A tapering course of corticosteroids as acute therapy for *Pneumocystis carinii* pneumonia (PCP) or other conditions is an exception and is allowed.

4.2.12 Any immunomodulator, HIV vaccine, live attenuated vaccines, or other investigational therapy or investigational vaccine within 30 days prior to study entry.

NOTE: Using G-CSF to increase neutrophil count prior to study entry is not permitted under this exclusion criterion.

4.2.13 Known allergy/sensitivity or any hypersensitivity to components of study drugs or their formulation.

4.2.14 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

4.2.15 Current or anticipated receipt of any of the prohibited medications listed in section 5.5.2.

4.2.16 In the opinion of the investigator, any psychological or social condition, or addictive disorder that would preclude compliance with the protocol.

4.3 Inclusion Criteria Step 2

4.3.1 **IERC-confirmed CR or PR** to the chemotherapy regimen used in Step 1.

4.3.2 **IERC-confirmed** KS progression at **least** 12 weeks after the last dose of Step 1 chemotherapy.

4.3.3 **Fewer than** 72 weeks after Step 1 entry.

4.3.4 The following laboratory values obtained within 14 days prior to Step 2 entry:

- ANC $\geq 1,000$ cells/mm³
- Hemoglobin ≥ 8.0 g/dL
- Platelet count $\geq 100,000$ /mm³
- Estimated creatinine clearance of ≥ 60 mL/min using the formula:
$$\text{CrCl} = \{[140 - \text{age (years)}] \times [\text{weight (kg)}]\} \div [72 \times \text{serum Cr (mg/dL)}]$$

(multiply the result x 0.85 for female participants)

NOTE: The Cockcroft-Gault calculation program can be found on DMC website (<http://www.fstrf.org/ACTG/index.html>).

- AST (SGOT), ALT (SGPT), and alkaline phosphatase $< 5 \times \text{ULN}$
- Total bilirubin of $\leq 1.5 \times \text{ULN}$

- 4.3.5 For females of reproductive potential, negative serum or urine pregnancy test within 7 days prior to Step 2 entry. The urine test must have a sensitivity of 15-25 mIU/mL.

NOTE: Females not of reproductive potential who do not have required documentation must also undergo pregnancy testing. Acceptable documentation of sterilization and menopause is specified in Appendix I and includes physician report.

- 4.3.6 Karnofsky performance status ≥ 50 within 28 days prior to Step 2.
- 4.3.7 All participants must agree not to participate in a conception process (active attempt to become pregnant or to impregnate, donate sperm, in vitro fertilization).
- 4.4 Exclusion Criteria Step 2
- 4.4.1 Current chronic, acute, or recurrent infections that are serious, in the opinion of the site investigator, for which the participant has not completed at least 14 days of therapy prior to Step 2 entry and/or is not clinically stable.
- 4.4.2 Severe toxicity to the chemotherapy regimen used in Step 1 requiring discontinuation of study chemotherapy.
- 4.4.3 Serious illness, other than progressive KS, requiring systemic treatment and/or hospitalization within 14 days prior to Step 2 entry.
- 4.4.4 For **participants** who received bleomycin in Step 1:
- Development of pulmonary fibrosis, COPD, emphysema, bronchiectasis, and diffuse or significant local radiographic interstitial infiltrates on CXR or CT scan that in the opinion of the site investigator would exclude bleomycin use.
 - Participants with an abnormal CXR or CT scan (which may indicate pulmonary KS) should undergo screening evaluations to rule out an infectious cause, per standard of care. If available, other diagnostic procedures such as bronchoscopy should be considered to confirm the presence or absence of pulmonary KS and/or an infectious agent. These procedures should be completed outside the study. These participants should be excluded if, in the opinion of the investigator, use of bleomycin in Step 2 would be detrimental.
 - Oxygen saturation less than 90% or exercise desaturation greater than 4% within the last 30 days prior to Step 2 entry.

NOTE: Individuals meeting any of the above exclusion criteria should be evaluated for eligibility to receive PTX in Step 3.

NOTE: Exercise is defined as any activity that will increase a participant's resting heart rate by 20 beats/minute.

- 4.4.5 For **participants** who received vincristine or PTX in Step 1, Grade ≥ 3 PN at Step 2 entry.

NOTE: Severity of PN will be determined by the symptom severity scores from the BPNS, discussed in section 6.3.20.

4.4.6 Breastfeeding.

4.4.7 Other concurrent chemotherapy, immunotherapy, or radiotherapy.

4.4.8 Systemic corticosteroid use at doses above those given as replacement therapy for adrenal insufficiency within 30 days of Step 2 entry.

NOTE: A tapering course of corticosteroids as acute therapy for PCP or if required for management of IRIS is an exception.

4.4.9 Receipt of ET in Step 1.

4.5 Inclusion Criteria Step 3

4.5.1 IERC-confirmed KS progression at any time during Step 1 chemotherapy OR

- IERC-confirmed KS progression **fewer than** 12 weeks after the last chemotherapy dose in Step 1 in participants who have had an **IERC-confirmed CR or PR** OR
- IERC-confirmed KS progression following Step 1 chemotherapy, without any prior response OR
- IERC-confirmed KS progression in Step 2 OR
- **With concurrence of the CMC**, there is dose-limiting toxicity after receiving **fewer than** four cycles of chemotherapy in Step 1 or Step 2, in the absence of a CR or PR **OR**
- Participants otherwise eligible for Step 2 who, in the opinion of the investigator **and with concurrence of the CMC**, are unlikely to benefit from another course of the same chemotherapy received in Step 1.

4.5.2 **Fewer than** 72 weeks after Step 1 entry.

4.5.3 The following laboratory values obtained within 14 days prior to Step 3 entry:

- ANC $\geq 1,000$ cells/mm³
- Hemoglobin ≥ 8.0 g/dL
- Platelet count $\geq 100,000$ /mm³
- Estimated creatinine clearance of ≥ 60 mL/min using the formula:
$$\text{CrCl} = \{[140 - \text{age (years)}] \times [\text{weight (kg)}]\} \div [72 \times \text{serum Cr (mg/dL)}]$$

(multiply the result x 0.85 for female participants)

NOTE: The Cockcroft-Gault calculation program can be found on DMC website (<http://www.fstrf.org/ACTG/index.html>).

- AST (SGOT), ALT (SGPT), and alkaline phosphatase $<5\times\text{ULN}$
- Total bilirubin of $\leq 1.5\times\text{ULN}$

4.5.4 For females of reproductive potential, negative serum or urine pregnancy test within 7 days prior to Step 3 entry. The urine test must have a sensitivity of 15-25 mIU/mL.

NOTE: Females not of reproductive potential who do not have required documentation must also undergo pregnancy testing. Acceptable documentation of sterilization and menopause is specified in Appendix I and includes physician report.

4.5.5 Karnofsky performance status ≥ 50 within 28 days prior to Step 3 entry.

4.5.6 All participants must agree not to participate in a conception process (active attempt to become pregnant or to impregnate, donate sperm, in vitro fertilization).

4.6 Exclusion Criteria Step 3

4.6.1 Current chronic, acute, or recurrent infections that are serious, in the opinion of the site investigator, for which the participant has not completed at least 14 days of therapy prior to Step 3 entry and/or is not clinically stable.

4.6.2 Serious illness, other than progressive KS, requiring systemic treatment and/or hospitalization within 14 days prior to Step 3 entry.

4.6.3 Eligible for Step 2 entry.

4.6.4 For **participants** who did NOT receive bleomycin in Step 1 or Step 2:

- Development of pulmonary fibrosis, COPD, emphysema, bronchiectasis, and diffuse or significant local radiographic interstitial infiltrates on CXR or CT scan that in the opinion of the site investigator would exclude bleomycin use.
- **Participants** with an abnormal CXR or CT scan (which may indicate pulmonary KS) should undergo screening evaluations to rule out an infectious cause, per standard of care. If available, other diagnostic procedures such as bronchoscopy should be considered to confirm the presence or absence of pulmonary KS and/or an infectious agent. These procedures should be completed outside the study. These participants should be excluded if, in the opinion of the investigator, use of bleomycin in Step 3 would be detrimental.
- Oxygen saturation less than 90% or exercise desaturation greater than 4% within the last 30 days prior to Step 3 entry.

NOTE: Exercise is defined as any activity that will increase a participant's resting heart rate by 20 beats/minute.

4.6.5 Grade ≥ 3 PN at Step 3 entry.

NOTE: Severity of PN will be determined by the symptom severity scores from the BPNS, discussed in section 6.3.20.

4.6.6 Breastfeeding.**4.6.7** Other concurrent chemotherapy, immunotherapy, or radiotherapy.**4.6.8** Systemic corticosteroid use at doses above those given as replacement therapy for adrenal insufficiency within 30 days of Step 3 entry.

NOTE: A tapering course of corticosteroids as acute therapy for PCP or if required for management of IRIS is an exception.

4.7 Inclusion Criteria Step 4**4.7.1**

- **IERC-confirmed KS progression in Step 3 OR**
- **With** concurrence **of the CMC**, dose-limiting toxicity after receiving **fewer than** four cycles of chemotherapy in Step 3, in the absence of a CR or PR **OR**
- **Current receipt of ET in Step 3**

4.7.2 **Fewer** than 72 weeks after Step 1 entry.**4.7.3** The following laboratory values obtained within 14 days prior to Step 4 entry:

- ANC $\geq 1,000$ cells/mm³.
- Hemoglobin ≥ 8.0 g/dL.
- Platelet count $\geq 100,000$ /mm³.
- Estimated creatinine clearance of ≥ 60 mL/min using the formula:
$$\text{CrCl} = \{[140 - \text{age (years)}] \times [\text{weight (kg)}]\} \div [72 \times \text{serum Cr (mg/dL)}]$$

(multiply the result x 0.85 for female participants)

NOTE: The Cockcroft-Gault calculation program can be found on DMC website (<http://www.fstrf.org/ACTG/index.html>).

- AST (SGOT), ALT (SGPT), and alkaline phosphatase $< 5 \times \text{ULN}$.
- Total bilirubin of $\leq 1.5 \times \text{ULN}$.

4.7.4 For females of reproductive potential, negative serum or urine pregnancy test within 7 days prior to Step 4 entry. The urine test must have a sensitivity of 15-25 mIU/mL.

NOTE: Females not of reproductive potential who do not have required documentation must also undergo pregnancy testing. Acceptable

documentation of sterilization and menopause is specified in Appendix I and includes physician report.

- 4.7.5 Karnofsky performance status ≥ 50 within 28 days prior to Step 4 entry.
- 4.7.6 All participants must agree not to participate in a conception process (active attempt to become pregnant or to impregnate, donate sperm, in vitro fertilization).

4.7.7 Receipt of ET in Step 1, Step 2, or Step 3.

4.8 Exclusion Criteria Step 4

- 4.8.1 Current chronic, acute, or recurrent infections that are serious, in the opinion of the site investigator, for which the participant has not completed at least 14 days of therapy prior to Step 4 entry and/or is not clinically stable.
- 4.8.2 Serious illness, other than progressive KS, requiring systemic treatment and/or hospitalization within 14 days prior to Step 4 entry.
- 4.8.3 For **participants** who did NOT receive bleomycin in Step 1, Step 2, or Step 3:
 - Development of pulmonary fibrosis, COPD, emphysema, bronchiectasis, and diffuse or significant local radiographic interstitial infiltrates on CXR or CT scan that in the opinion of the site investigator would exclude bleomycin use.
 - **Participants** with an abnormal CXR or CT scan (which may indicate pulmonary KS) should undergo screening evaluations to rule out an infectious cause, per standard of care. If available, other diagnostic procedures such as bronchoscopy should be considered to confirm the presence or absence of pulmonary KS and/or an infectious agent. These procedures should be completed outside the study. These participants should be excluded if, in the opinion of the investigator, use of bleomycin in Step 4 would be detrimental.
 - Oxygen saturation less than 90% or exercise desaturation greater than 4% within the last 30 days prior to Step 4 entry.

NOTE: Exercise is defined as any activity that will increase a participant's resting heart rate by 20 beats/minute.

- 4.8.4 Grade ≥ 3 PN at Step 4 entry.

NOTE: Severity of PN will be determined by the symptom severity scores from the BPNS, discussed in section 6.3.20.

- 4.8.5 Breastfeeding.
- 4.8.6 Other concurrent chemotherapy, immunotherapy, or radiotherapy.
- 4.8.7 Systemic corticosteroid use at doses above those given as replacement therapy for adrenal insufficiency within 30 days of Step 4 entry.

NOTE: A tapering course of corticosteroids as acute therapy for PCP or if required for management of IRIS is an exception.

4.9 Study Enrollment Procedures

- 4.9.1 Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS Protocol Registration Office (DAIDS PRO) and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable regulatory entities (RE) approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICFs WILL NOT be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

4.9.2 Protocol Activation

Prior to enrollment, sites must complete the Protocol Activation Checklist found on the ACTG Member website. This checklist must be approved prior to any screening of participants for enrollment.

4.9.3 Randomization

For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the initial protocol step, an ACTG Screening Failure Results form must be completed and keyed into the database.

Participants who meet eligibility criteria for A5263/AMC066 will be registered to the study according to standard ACTG Data Management Center procedures.

4.10 Co-enrollment Guidelines

- Sites are strongly encouraged to co-enroll participants in stand-alone substudy A5278s, "Pharmacology Substudies of A5263 and A5264." Co-enrollment in A5278s does not require permission from the A5263/AMC066 protocol chairs.

- Sites are strongly encouraged to co-enroll participants in A5243, “Plan for Obtaining Human Biological Samples at Non-US Clinical Research Sites for Currently Unspecified Genetic Analyses.” Co-enrollment in A5243 does not require permission from the A5263/AMC066 protocol chairs.
- For specific questions and approval for co-enrollment in other studies, sites must contact the protocol chairs via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

Study-provided medications are **ET**, bleomycin sulfate, vincristine sulfate, PTX, FTC/TDF (Truvada®), EFV (Stocrin®), and EFV/FTC/TDF (Atripla®).

ET, bleomycin sulfate, vincristine sulfate, and PTX are FDA Pregnancy Category D.

Study treatment is considered **any of the premedications for chemotherapy**, any of the chemotherapy regimens plus study-provided ART or an approved, non-study-provided ART regimen.

Participants will have access to local standard of care ART and chemotherapy through local treatment programs available at the sites following study week 96. As part of their site implementation plan (SIP), sites **are** required to demonstrate that they have developed the appropriate relationship with local treatment programs to provide the local standard of care for ART and chemotherapy. Please refer to the A5263/AMC066 PSWP for the detailed SIP.

5.1 Regimens, Administration, and Duration

Detailed instructions for administration of the chemotherapeutic study products used in this study and premedication and antiemetic guidelines are given in the A5263/AMC066 MOPS.

5.1.1 Step 1

At entry, participants will be randomized in a 1:1 ratio to receive ART with EFV/FTC/TDF (Atripla®) plus **either treatment regimen 1B or 1C as listed below.**

5.1.1.1 Chemotherapeutic Agents

Treatment Arm	Study Product	Dosage	Route/Time	Frequency/Duration
1A	Etoposide (ET)	Initiation of ET in all steps was discontinued as of March, 2016. The following treatment instructions are provided for		

Treatment Arm	Study Product	Dosage	Route/Time	Frequency/Duration
		participants currently receiving ET in any step who elect to complete their current course of ET: 50 mg orally twice daily (with escalation on subsequent cycles up to a maximum of 100 mg twice daily, depending on toxicity) for 7 consecutive days of every 3-week cycle for maximum of six cycles at the highest dose achieved.		
1B	Vincristine sulfate (V)	2 mg/2mL solution	IV over 1 minute (maximum 5 minutes)⁴	Every 3 weeks for up to six cycles
	Bleomycin sulfate (B)	15 units/m ² in 50 mL 0.9% sodium chloride for injection ¹	IV over 10 minutes (maximum 60 minutes)⁴	Every 3 weeks for up to six cycles
1C	Paclitaxel (PTX)	100 mg/m ² in 200 mL, 250 mL, or 500 mL of 5% dextrose or 0.9% sodium chloride for injection ^{1,2,3}	IV over 1 hour (maximum 3 hours) using non-PVC administration set and ≤0.22 micron inline-filter ⁴	Every 3 weeks for up to six cycles

¹ The dose of bleomycin and PTX to be administered will be calculated based on body surface area expressed in square meters (m²). See the PSWP for further instructions

² The final concentration of prepared PTX injection in 5% dextrose or 0.9% sodium chloride for IV administration must be between 0.3 to 1.2 mg/mL.

³ Premedication MUST be given prior to administration of each dose of PTX. Please refer to the **A5263/AMC066** MOPS for instructions on the drugs, dosages, and timing of premedication.

⁴ The preferred time for IV infusions is as shown, but may, if necessary, be prolonged up to the maximum duration as noted in parentheses under the "Route/Time" column for each IV study product. Deviations from these lower and upper ranges must be reported and explained.

5.1.1.2 Etoposide (ET)

Initiation of ET in all steps was discontinued in March 2016. The following treatment instructions are provided for participants currently receiving ET in any step who elect to complete their current course of ET:

Beginning on day one of the chemotherapy cycle, ET will be given orally in a dose of 50 mg twice daily for 7 consecutive days for the first cycle. If there is no Grade ≥2 toxicity attributable to ET after the first cycle, the dose will be escalated to 150 mg daily for 7 days in divided doses of 100 mg/50 mg for the second cycle. After the second cycle, if there is no

Grade ≥ 2 toxicity attributable to ET, the dose will be escalated to 100 mg twice daily for 7 days for the third and subsequent cycles. ET should be taken on an empty stomach. Because there is no information concerning the administration of ET and didanosine (DDI), if a participant is also taking DDI, it is preferable that ET and DDI not be given within 2 hours of each other.

Each cycle of ET should begin 21 days (± 2 days) after the first day of the previous cycle. A new cycle of ET must not be started earlier than 19 days after the first dose of the previous cycle.

Treatment with ET will continue for six cycles at the maximum **tolerated dose** or until toxicity requiring discontinuation of study chemotherapy, or the site investigator, after consulting with the CMC, has determined that alternative therapy is required, whichever occurs first.

If ET dose reduction is required after dose escalation, any cycles administered at a higher dose will be counted as part of the six cycles at the maximum tolerated dose. Under no circumstances should participants receive a total of more than eight cycles of ET. No ET will be administered after week 96. Any unused ET returned by the participant should be returned to the pharmacy.

See section 7.0 for ET dosage modifications.

5.1.1.3 Bleomycin and Vincristine (BV)

BV will be administered on day one of each chemotherapy cycle.

5.1.1.3.1 Vincristine sulfate will be administered at a dose of 2 mg (fixed dose) in a volume of 2 mL over 1 minute (**see section 5.1.1 for note regarding acceptable IV infusion times**) into the sidearm of a rapidly flowing intravenous infusion every 3 weeks (**± 2 days**) (see section 7.0 for specific instructions regarding dosage reduction for participants with elevated bilirubin or AST). The vincristine infusion will be followed by bleomycin as detailed below.

5.1.1.3.2 Bleomycin sulfate will be administered at a dose of 15 units/m² over 10 minutes (**see section 5.1.1 for note regarding acceptable IV infusion times**) every 3 weeks (**± 2 days**) (see section 7.0 for specific instructions regarding dosage reduction for participants whose creatinine clearance falls below 60 mL/min).

Maximum cumulative lifetime total dose of bleomycin is 400 units.

See section 7.0 for specific instructions regarding bleomycin dosage modification for participants with reduced creatinine clearance.

5.1.1.3.3 BV will be administered on **day one** of each 3-week cycle.

Each cycle of BV should be administered 21 days (± 2 days) after the first day of the previous cycle. BV must not be administered earlier than 19 days after the previous cycle.

Treatment with BV will continue for six cycles, or until toxicity requiring discontinuation of study chemotherapy, or the site investigator, after consulting with the CMC, has determined that alternative therapy is required, whichever occurs first.

5.1.1.4 Paclitaxel Injection (PTX)

PTX will be administered by IV infusion in 200 mL, 250 mL, or 500 mL of 5% dextrose or 0.9% sodium chloride for injection at a dose of 100 mg/m² every 3 weeks (± 2 days).

The concentrated PTX solution in vial must be diluted prior to use in 5% dextrose or 0.9% **sodium chloride** to a final concentration of 0.3 to 1.2 mg/mL prior to infusion.

Avoid excessive agitation, vibration, or shaking of the IV solution for infusion.

Flush the infusion sets thoroughly before use.

Regularly inspect the appearance of the infusion and stop the infusion if precipitation is present.

PTX injection for infusion must be administered through an appropriate in-line filter with microporous membrane of ≤ 0.2 micrometers. DEHP-free infusion containers and administration sets must be used. Use of filter devices which incorporate short inlet and/or outlet plasticized tubing has not resulted in significant leaching of DEHP.

The entire dose should be infused in one hour (**see section 5.1.1.1 for note regarding acceptable IV infusion times**).

Each cycle of PTX should be administered 21 days (± 2 days) after the first day of the previous cycle. PTX must not be administered earlier than 19 days after the previous cycle.

Treatment with PTX will continue for six cycles, or until toxicity requiring discontinuation of study chemotherapy, or the site investigator, after consulting with the CMC, has determined that alternative therapy is required whichever occurs first.

See section 7.0 for specific instructions regarding PTX dosage modifications.

NOTE: Do not administer as a bolus injection or an undiluted solution.

5.1.1.5 Antiretroviral Therapy

The study will provide ART until week 96 after Step 1 Randomization.

The study will provide EFV/FTC/TDF (Atripla®) which is the preferred ART regimen. If there is a contraindication to EFV, participants must have access to an alternative NNRTI or protease inhibitor/ritonavir (PI/r) provided from outside of the study.

The following ART regimens may be used:

- EFV/FTC/TDF (Atripla®) 200 mg/300 mg/600 mg orally once daily on an empty stomach, preferably at bedtime **OR**
- FTC/TDF 200 mg/300 mg (Truvada®) orally once daily at bedtime plus EFV (Stocrin®) 600 mg orally once daily at bedtime **OR**
- FTC/TDF 200 mg/300 mg (Truvada®) orally once daily plus NVP 200 mg orally twice daily **OR**
- FTC/TDF 200 mg/300 mg (Truvada®) orally once daily plus PI/r at standard dosing

See section 7.0 for ART dosage modifications.

NOTE A: For participants taking EFV it is recommended that the ART regimen be taken at bedtime, although this is not required.

NOTE B: Women taking EFV and who are of reproductive potential are required to use two methods of acceptable birth control, and they will be asked if they are using two methods of birth control at every visit, starting at the week 3 visit. If a woman reports she is not using two acceptable methods of birth control, EFV will be replaced with NVP or PI/r. Record the drug substitution and reason in the source documents and record the drug substitution on the case report form (CRF).

NOTE C: NVP should be started with the lead-in of 200 mg orally once daily for 14 days; then 200 mg orally twice daily. Health care providers must review signs and symptoms of NVP-related hypersensitivity and hepatitis with the participant prior to dispensing NVP. Participants

should contact their site physician if they develop rash or signs and symptoms of hypersensitivity or hepatitis. If rash occurs during lead-in, do not increase dose until the rash has resolved. The lead-in dosing period should not exceed 28 days. After reaching full dose, if NVP dosing is interrupted for >7 days, then NVP should be started with the lead-in of 200 mg orally once daily for 14 days, followed by 200 mg orally twice daily. The risk of hepatotoxicity in women with CD4+ lymphocyte cell counts >250 cells/mm³, including pregnant women receiving chronic treatment for HIV infection, is considerably higher (12-fold) compared with women with CD4+ lymphocyte cell counts ≤250 cells/mm³ (11% versus 0.9%). Men with higher CD4+ lymphocyte cell counts (>400 cells/mm³) also have a higher risk of hepatotoxicity than men with lower CD4+ cell counts (6.3% versus 1.2%).

NOTE D: Please be advised that didanosine (ddI)- and stavudine (d4T)-associated neuropathy may be worsened by co-administration of vincristine.

NOTE E: Chemotherapy-associated anemia and neutropenia may be worsened by co-administration of ZDV.

NOTE F: Participants who have suspected or confirmed resistance to NNRTI, including female participants who have previously received single-dose NVP for prevention of MTCT of HIV, should receive:

- TDF/FTC + PI/r if they are randomized to receive either ET or PTX.
- Either ABC/3TC/ZDV, or TDF/FTC+ZDV, or a non-ritonavir-boosted PI + two NRTIs if they are randomized to receive BV.

5.1.2 Steps 2, 3, and 4

A new prescription must be written for the site pharmacist to dispense study-products. The site pharmacist must receive a new Study Identification number (SID) when registering participants to each step.

5.2 Study Product Preparation

5.2.1 Bleomycin

5.2.1.1 Reconstitution of Lyophilized Product

Hospira product: Hospira's formulation of bleomycin is packaged as 30 Units of lyophilized powder per vial. Using aseptic technique, reconstitute each vial with 10 mL of 0.9% sodium chloride for injection to yield 3 Units/mL (30 Units/ 10 mL) solution.

Amneal product: Amneal's formulation of bleomycin is packaged as 15 Units of lyophilized powder per vial. Using aseptic technique,

reconstitute each vial with 5 mL of 0.9% sodium chloride for injection to yield 3 Units/mL (15 Units/ 5 mL) solution.

Locally-sourced formulations of bleomycin: The locally-available formulations of bleomycin are packaged as 15 Units of lyophilized powder per vial. Instructions for reconstitution described for the Amneal product above should be followed. If these reconstitution and preparation instructions are not in accordance with the package insert of the locally-sourced bleomycin, then the site should submit the package insert and proposed preparation instructions to the protocol team for review and approval prior to use.

- 5.2.1.2 Withdraw study participant's calculated dose of bleomycin in mL from the reconstituted bleomycin vial(s) into a syringe and inject it into a 50 mL 0.9% sodium chloride for injection IV bag.
- 5.2.1.3 Administer the prepared bleomycin in 50 mL 0.9% sodium chloride for injection IV bag by IV infusion over 10 minutes (see section 5.1.1.1 for note regarding acceptable IV infusion times).
- 5.2.1.4 **Hospira's bleomycin prepared in 50 mL 0.9% sodium chloride IV bag for infusion is stable for up to 24 hours at room temperature, 15-30 °C (59-86°F).**

Amneal's bleomycin prepared in 50 mL 0.9% sodium chloride IV bag for infusion is stable for up to 24 hours when stored in the dark at refrigerated temperature, 2-8°C (36-46°F).

Locally-sourced bleomycin prepared in 50 mL 0.9% sodium chloride IV bag for infusion should be stored up to the duration in time and within specified storage temperature range as directed by the manufacturer in the package insert.

- 5.2.1.5 Do not use if a precipitate, foreign matter, or discoloration is present.
- 5.2.1.6 Bleomycin for injection should not be reconstituted or diluted with 5% dextrose for injection or other dextrose-containing diluents, as loss of potency can occur.
- 5.2.1.7 Do not mix bleomycin with other drugs or solutions, as compatibility is unknown.
- 5.2.1.8 Caution should be exercised in handling bleomycin. The use of gloves and gown is recommended. If bleomycin comes in contact with the skin or mucosa, immediately wash thoroughly with soap and water.

- 5.2.1.9 Discard any unused solution according to proper handling and disposal procedures for anti-cancer drugs.

5.2.2 Vincristine

- 5.2.2.1 Using aseptic technique, withdraw 2 mL from a vial of vincristine containing 2mg/2mL into a syringe and cap.
- 5.2.2.2 Vincristine prepared in a syringe should be administered as soon as prepared.
- 5.2.2.3 Do not use if a precipitate, foreign matter or discoloration is present.
- 5.2.2.4 Caution should be exercised in handling vincristine. The use of gloves and gown is recommended. If vincristine comes in contact with the skin or mucosa, immediately wash thoroughly with soap and water.
- 5.2.2.5 Do not mix vincristine with other drugs or solutions, as compatibility is unknown.
- 5.2.2.6 Discard any unused solution according to proper handling and disposal procedures for anti-cancer drugs.
- 5.2.2.7 Include on the prepared vincristine study product label "FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY".
- 5.2.2.8 Administer IV over 1 minute (see section **5.1.1.1** for note regarding acceptable IV infusion times).

Vincristine must be administered via an intact free-flowing intravenous needle or into the tubing of a running intravenous infusion and then flushed with the IV fluid being administered. Care should be taken that no leakage or swelling occurs during administration. If any leakage or swelling occurs during administration, the injection should be discontinued immediately and any remaining portion of the dose should then be introduced into another vein. Please refer to the **A5263/AMC066** MOPS for additional recommendations on the management of chemotherapy extravasation.

- 5.2.2.9 Vincristine should be administered before bleomycin if given in the same IV line.

5.2.3 PTX Injection

- 5.2.3.1 Premedication **MUST** be given prior to administration of each dose of PTX. Please refer to the **A5263/AMC066** MOPS for instructions on the drugs, dosages and timing of premedication.

- 5.2.3.2 **PTX** is dosed 100 mg/m² IV over 1 hour (see section **5.1.1.1** for note regarding acceptable IV infusion times) every 3 weeks. Do not administer as a bolus injection.
- 5.2.3.3 Using aseptic technique, withdraw study participant's calculated dose in mL from **PTX** injectable vial.
- 5.2.3.4 Do not use the Chemo-Dispensing Pin device or similar device with spikes since they can cause the vial stopper to collapse, resulting in loss of sterile integrity.
- 5.2.3.5 **PTX** must be diluted in 200 mL, 250 mL, or 500 mL of 5% dextrose for injection or 0.9% sodium chloride for injection in polypropylene or polyolefin plastic bag (DEHP-free infusion containers) or a glass bottle.
- 5.2.3.6 The final concentration of prepared **PTX** injection in 5% dextrose or 0.9% sodium chloride for IV administration must be between 0.3 to 1.2 mg/mL.
- 5.2.3.7 Solutions for infusion prepared as above should be used immediately. If not used immediately, the solution for infusion can be stored in a refrigerator between 2-8°C (36-46°F) for up to 24 hours.
- 5.2.3.8 Do not use if the prepared solution for infusion is cloudy or an insoluble precipitate is present.
- 5.2.3.9 Caution should be exercised in handling **PTX** solution. The use of gloves and gown is recommended. If **PTX** comes in contact with the skin or mucosa, immediately wash thoroughly with soap and water.
- 5.2.3.10 Do not mix **PTX** with other drugs or solutions, as compatibility is unknown.
- 5.2.3.11 Discard any unused solution according to proper handling and disposal procedures for chemotherapeutic products.
- 5.2.3.12 To avoid participant exposure to plasticizer leached from polyvinyl chloride (PVC), **PTX** must be prepared in polypropylene or polyolefin plastic bag (DEHP-free infusion containers) or a glass bottle and infused through a non-PVC containing administration set with an inline filter with a micro porous membrane not greater than 0.2 microns.
- 5.2.3.13 **PTX** is considered an irritant with vesicant potential. Care should be taken that no leakage or swelling occurs during administration. If any leakage or swelling occurs during administration, the injection should be discontinued immediately and any remaining portion of the dose should then be introduced into another vein. **Please refer to the**

A5263/AMC066 MOPS for additional recommendations on the management of chemotherapy extravasation.

5.3 Study Product Formulation and Storage

Study Product	Formulation	Storage
Etoposide (ET)	50 mg soft gelatin capsule	Do not store above 25°C (77°F)
Bleomycin sulfate injection (B) manufactured by Hospira	30 units powder per single use vial	Store between 2-8°C (36-46°F) Protect from light. Store vials upright.
Bleomycin sulfate injection (B) manufactured by Amneal	15 units powder per single use vial (15,000 IU powder per single use vial, 1,000 IU = 1 unit)	Store between 2-8°C (36-46°F) (Refrigerate. Do not freeze.)
Bleomycin sulfate injection (B) locally-sourced	15 units powder per single use vial	Store within the specified storage temperature range as directed by the manufacturer in the package insert
Vincristine sulfate injection (V)	2 mg/ 2 mL solution per single use vial (1 mg/mL)	Store between 2-8°C (36-46°F) Protect from light. Store vials upright.
Paclitaxel injection (PTX)	6 mg/mL solution per vial (for single use only in this study). The other ingredients contained in PTX solution are polyoxyl castor oil and ethanol.	Do not store above 25°C (77°F). Store the vial in the original, outer carton to protect from light.
Emtricitabine/ Tenofovir Disoproxil Fumarate (FTC/TDF) (Truvada®)	200 mg/300 mg tablet	Store at 25°C (77°F); excursions permitted between 15-30°C (59-86°F). Keep container tightly closed. Dispense only in original container.
EFV (Stocrin®)	600 mg tablet	Store at 15-30°C (59-86°F). Each bottle contains a silica gel desiccant canister that should remain in the original container to protect the product from humidity.
EFV/FTC/TDF (Atripla®)	600 mg/200 mg/300 mg tablet	Store up to 30°C (86°F).

5.4 Study Product Supply, Acquisition, and Accountability

5.4.1 Study Product Supply

5.4.1.1 Etoposide soft gelatin capsules **are** supplied by Bristol-Myers Squibb.

5.4.1.2 Bleomycin sulfate injection manufactured by **either Hospira or Amneal Biosciences** is supplied through the study with funding support from the ACTG.

In the event that bleomycin sulfate injection manufactured by either Hospira or Amneal Biosciences is not available from the CRPMC, study sites may source bleomycin locally until either Hospira's or Amneal's bleomycin can be provided through the study. Available local sources of bleomycin at each of the study sites are shown in the following table:

CRS Number CRS Name Country	Locally-Available Bleomycin Injection Formulations
11101 Wits Helen Joseph Hospital CRS South Africa	Bleolem, by Teva Pharmaceuticals, 15 units/vial
11201 Durban International CRS South Africa	Teva Bleomycin, by Teva Pharmaceuticals, 15 units/vial Bleolem, by Lemery, 15 units/vial
12001 Malawi CRS Malawi	Bleomycin Injection, by Celon Labs and United Biotech Limited, 15 units/vial
12101 Instituto De Pesquisa Clinica Evandro Chagas CRS Brazil	Bleomycin Sulfate, by Meizler Biopharma, 15 units/vial
12501 KEMRI/WRP CRS Kenya	Bleochem, by Biochem Ltd, 15 units/vial, lyophilized
12601 Moi University CRS Kenya	Bleochem, by Biochem Ltd, 15 units/vial Lyoble, by United Biotech, 15 units/vial
30301 Blantyre CRS Malawi	Bleomycin Sulfate Injection, by Angel Biogenics, 15 units/vial
30313 Parirenyatwa CRS Zimbabwe	Bleomycin Injection, by Celon Labs, 15 units/vial

CRS Number CRS Name Country	Locally-Available Bleomycin Injection Formulations
31460 Kisumu CRS Kenya	Bemocin, by Fresenius, 15 units/vial
31713 Uganda Cancer Institute CRS Uganda	Bleomycine-Bellon, by Sanofi-Aventis, 15 units/vial Bloicin-S, by Korea United Pharm. Inc, 15 units/vial
8950 FAM-CRU CRS South Africa	Bleolem, by Key Oncologies, 15 units/vial Blenamax, by Pharmachemie, 15 units/vial

5.4.1.3 Vincristine sulfate injection manufactured by Hospira **is** supplied through the study with funding support from the ACTG.

5.4.1.4 Paclitaxel injection manufactured **by** Accord Healthcare Limited **is supplied through the study** with funding support from the ACTG.

5.4.1.5 FTC/TDF (Truvada®) tablets **are** provided by Gilead Sciences.

5.4.1.6 Efavirenz (Stocrin®) tablets **are** provided by Merck.

5.4.1.7 EFV/FTC/TDF (Atripla®) tablets **are** provided by Merck.

5.4.1.8 If bleomycin and vincristine supplied through the study are not manufactured by Hospira (bleomycin and vincristine) or Amneal (bleomycin only), then the study product that will be provided through the study must comply with the NIAID (DAIDS) policy for the use of study products not marketed in the US in NIAID (DAIDS)-supported and/or sponsored clinical trials. This policy is available on the NIAID (DAIDS) website at:
<https://www.niaid.nih.gov/sites/default/files/NonFDAApprovedProducts.pdf>.

5.4.2 Study Product Acquisition

ET, bleomycin sulfate, vincristine sulfate, PTX, FTC/TDF (Truvada®), EFV (Stocrin®), and EFV/FTC/TDF (Atripla®) are available through the NIAID Clinical Research Products Management Center (CRPMC). The ACTG site pharmacists can obtain study products for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section Study Product Management Responsibilities.

In the event that bleomycin is not available from the CRPMC, sites should source drug locally as described in 5.4.1.2.

5.4.3 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. The site pharmacist at non-US *clinical* research sites must follow the instructions in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks DAIDS Pharmaceutical Affairs for the destruction of unused study products.

5.5 Concomitant Medications

Below is the list of selected concomitant medications. These lists are only current as of the date of this protocol. Therefore, whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medications' and study agents' most recent package inserts, Investigator's Brochures, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

5.5.1 Required Medications

All study participants are required to take ART, see section 5.1 for details.

5.5.2 Prohibited and Precautionary Medications

For the list of prohibited and precautionary medications, please refer to the A5263/AMC066 PSWP: (<https://member.actgnetwork.org/study/51726#profile=3>).

Click on the A5263 PSWP tab and then go to the Current Study-Specific Support Documents folder.

5.6 Adherence Assessment

See sections 6.3.21 and 6.3.22.

6.0 CLINICAL AND LABORATORY EVALUATIONS**6.1 Schedule of Events****6.1.1 Step 1–Screening to Week 24**

Evaluation	Screen	Entry	Step 1 Post-Entry Evaluations (Weeks)									Virologic Failure	KS-IRIS
			3	24–48 Hours after Second Chemotherapy Cycle Begins	6	9	12	15	18	21	24		
Documentation of HIV-1	X												
Biopsy Diagnostic of KS (Fixed in Formalin)	X		Repeat a diagnostic biopsy for KS to confirm a complete KS response ¹										
Documentation of KS Stage T1	X												
Documentation of KS Cutaneous Marker Lesions	X												
Medical/ Medication History	X	X											
Concomitant Medications		X	X		X	X	X	X	X	X	X		X
Complete Physical Exam	X												
Body Surface Area Calculation		X	Recalculate if a participant's weight has changed by 10% or more after Step 1 entry for re-calculation of bleomycin and PTX doses										
Targeted Physical Exam		X	X		X	X	X	X	X	X	X		X
Clinical Assessment	X	X	X		X	X	X	X	X	X	X		X
KS Exam		X	X		X	X	X	X	X	X	X		X
Photographic Record		X	Obtain for a change in KS response category										
KS Tumor Punch Biopsy for Storage in RNAlater		X		X									X
CD4+/CD8+	X	X					X				X		X
HIV-1 RNA		X					X				X	X	X
Stored Serum for Protocol-Related Research		X	X	X			X				X		X

Evaluation	Screen	Entry	Step 1 Post-Entry Evaluations (Weeks)									Virologic Failure	KS-IRIS
			3	24–48 Hours after Second Chemotherapy Cycle Begins	6	9	12	15	18	21	24		
Stored Plasma for Protocol-Related Research		X	X	X			X				X		X
Stored PBMC for Protocol-Related Research		X	X	X			X				X		X
Hematology	X	X	X		X	X	X	X	X	X	X		
Chemistries	X	X	X		X	X	X	X	X	X	X		
HBsAg		X											
Lactate	Perform for symptoms suggestive of lactic acidosis												
Lipase & Triglycerides	Perform for symptoms suggestive of pancreatitis												
Creatine Kinase	Perform for symptoms suggestive of myopathy												
Urinalysis		X											
Pregnancy Testing	X	X	Perform prior to a new chemotherapy cycle and whenever pregnancy is suspected										
CXR	X	Repeat at the time of suspected or IERC-confirmed KS progression or entry into the next step. For participants with known pulmonary KS at entry, a CXR will be repeated every third cycle.											X
Pulse Oximetry	X	X ²	X ²		X ²	X ²	X ²	X ²	X ²	X ²	X ²		
Peripheral Neuropathy Assessment	X		X ³		X ³	X	X ³	X ³	X ³	X			
ART Adherence Assessment					X		X		X				X
ET Adherence Assessment			X ⁴		X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴		X ⁴
Quality of Life Assessment		X					X				X		

¹ A confirmatory biopsy is required **only for** participants in whom hyperpigmented macular skin lesions persist after apparent CR.

² Complete only if the participant is receiving bleomycin.

³ Complete only if the participant is receiving vincristine or PTX.

⁴ Only complete if a participant is receiving ET.

6.1.2 Step 1–Week 27 to Discontinuation Evaluations

Evaluation	Step 1 Post-Entry Evaluations (Weeks)										Discontinuation Evaluations	Virologic Failure
	27	30	33	36	39	42	45	48	60-96 (Follow-up Every 12 Weeks) ²	E + 144 ³		
Biopsy Diagnostic of KS (Fixed in Formalin)	Repeat a diagnostic biopsy for KS to confirm a complete KS response ¹											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Targeted Physical Exam	X	X	X	X	X	X	X	X	X		X	
Clinical Assessment	X	X	X	X	X	X	X	X	X	X	X	
KS Exam	X	X	X	X	X	X	X	X	X		X	
Photographic Record	Obtain for a change in KS response category										X	
CD4+/CD8+				X				X	X		X	
HIV-1 RNA				X				X	X		X	X
Stored Serum, Plasma, PBMC for Protocol-Related Research								X			X	
Hematology	X			X				X	X	X	X	
Chemistries	X			X				X	X		X	
Lactate	Perform for symptoms suggestive of lactic acidosis											
Lipase & Triglycerides	Perform for symptoms suggestive of pancreatitis											
Creatine Kinase	Perform for symptoms suggestive of myopathy											
Urinalysis											X	
Pregnancy Testing	Perform prior to a new chemotherapy cycle and whenever pregnancy is suspected										X	

Evaluation	Step 1 Post-Entry Evaluations (Weeks)										Discontinuation Evaluations	Virologic Failure
	27	30	33	36	39	42	45	48	60-96 (Follow-up Every 12 Weeks) ²	E + 144 ³		
CXR	Repeat at the time of suspected or IERC-confirmed KS progression or entry into the next step. For participants with known pulmonary KS at entry, a CXR will be repeated on every third cycle.											
Pulse Oximetry	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	
ART Adherence Assessment		X						X	X		X	
Quality of Life Assessment								X			X	

¹ A confirmatory biopsy is required **only for** participants in whom hyperpigmented macular skin lesions persist after apparent CR.

² **If conducted on Step 1, week 96 is the last visit for participants in Arm 1B or 1C.**

³ **E=week the last cycle of ET was started. The E+144 visit will only be conducted for participants in Arm 1A who are still on Step 1.**

⁴ Complete only if the participant is receiving bleomycin.

6.1.3 Step 2, Step 3, and Step 4—Randomization to Week 27

Evaluation	Entry (R)	Step 2 Post-Entry Evaluations (Weeks)										
		R + 3	24–48 Hours after Second Chemotherapy Cycle Begins	R + 6	R + 9	R + 12	R + 15	R + 18	R + 21	R + 24	R + 27	Virologic Failure
Biopsy Diagnostic of KS (Fixed in Formalin)		Repeat a diagnostic biopsy for KS to confirm a complete KS response ¹										
Concomitant Medications	X	X		X	X	X	X	X	X	X	X	
Targeted Physical Exam	X	X		X	X	X	X	X	X	X	X	
Body Surface Area Calculation	Recalculate if a participant's weight has changed by 10% or more after Step 1 entry for re-calculation of bleomycin and PTX doses											
Clinical Assessment	X	X		X	X	X	X	X	X	X	X	
KS Exam	X	X		X	X	X	X	X	X	X	X	
Photographic Record	X	Complete for a change in KS response category										
KS Tumor Punch Biopsy for Storage in RNA later	X ²		X ²									
CD4+/CD8+	X					X				X		
HIV-1 RNA	X					X				X		X
Stored Serum for Protocol-Related Research	X	X	X			X				X		
Stored Plasma for Protocol-Related Research	X	X	X			X				X		
Stored PBMC for Protocol-Related Research	X	X	X			X				X		
Hematology	X	X		X	X	X	X	X	X	X	X	
Chemistries	X	X		X	X	X	X	X	X	X	X	
Lactate	Perform for symptoms suggestive of lactic acidosis											
Lipase & Triglycerides	Perform for symptoms suggestive of pancreatitis											
Creatine Kinase	Perform for symptoms suggestive of myopathy											

Evaluation	Entry (R)	Step 2 Post-Entry Evaluations (Weeks)										
		R + 3	24–48 Hours after Second Chemotherapy Cycle Begins	R + 6	R + 9	R + 12	R + 15	R + 18	R + 21	R + 24	R + 27	Virologic Failure
Pregnancy Testing	Perform prior to a new chemotherapy cycle and whenever pregnancy is suspected											
CXR	Repeat at the time of suspected or IERC-confirmed KS progression or entry into the next step. For participants with known pulmonary KS at entry or at the time of entry into Step 2 or Step 3, a CXR will be repeated on every third cycle.											
Pulse Oximetry	X ³	X ³		X³	X ³	X ³	X ³	X ³	X ³	X ³	X ³	
Peripheral Neuropathy Assessment	X	X ⁴		X ⁴	X	X ⁴	X ⁴	X ⁴	X			
ART Adherence Assessment	X			X		X		X				
ET Adherence Assessment		X ⁵		X ⁵	X ⁵	X ⁵	X ⁵	X ⁵	X ⁵	X ⁵		
Quality of Life Assessment	X					X				X		

¹ A confirmatory biopsy is required **only for** participants in whom hyperpigmented macular skin lesions persist after apparent CR.

² These biopsies are strongly encouraged.

³ Complete only if the participant is receiving bleomycin.

⁴ Complete only if the participant is receiving vincristine or PTX.

⁵ Only complete if a participant is receiving ET.

6.1.4 Step 2, Step 3, and Step 4—Week 30 to Discontinuation Evaluations

Evaluation	Step 2 Post-Entry Evaluations (Weeks)									Discontinuation Evaluations	Virologic Failure
	R + 30	R + 33	R + 36	R + 39	R + 42	R + 45	R + 48	R+60 — R+96 (Follow-up Every 12 Weeks)	E + 144 ²		
Biopsy Diagnostic of KS (Fixed in Formalin)	Repeat a diagnostic biopsy for KS to confirm a complete KS response ¹										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
Targeted Physical Exam	X	X	X	X	X	X	X	X		X	
Clinical Assessment	X	X	X	X	X	X	X	X	X	X	
KS Exam	X	X	X	X	X	X	X	X		X	
Photographic Record	Complete for a change in KS response category									X	
CD4+/CD8+			X				X	X		X	
HIV-1 RNA			X				X	X		X	X
Stored Serum, Plasma, PBMC for Protocol-Related Research							X			X	
Hematology			X				X	X	X	X	
Chemistries			X				X	X		X	
Lactate	Perform for symptoms suggestive of lactic acidosis										
Lipase & Triglycerides	Perform for symptoms suggestive of pancreatitis										
Creatine Kinase	Perform for symptoms suggestive of myopathy										
Urinalysis										X	
Pregnancy Testing	Perform prior to a new chemotherapy cycle and whenever pregnancy is suspected									X	
CXR	Repeat at the time of suspected or IERC-confirmed KS progression or entry into the next step. For participants with known pulmonary KS at entry or at the time of entry into Step 2 or Step 3, a CXR will be repeated on every third cycle.										

Evaluation	Step 2 Post-Entry Evaluations (Weeks)									Discontinuation Evaluations	Virologic Failure
	R + 30	R + 33	R + 36	R + 39	R + 42	R + 45	R + 48	R+60 — R+96 (Follow-up Every 12 Weeks)	E + 144 ²		
Pulse Oximetry	X ³	X ³	X ³	X ³	X ³	X ³	X ³	X ³	X ³	X ³	
ART Adherence Assessment	X						X	X		X	
Quality of Life Assessment							X			X	

¹ A confirmatory biopsy is required **only for** participants in whom hyperpigmented macular skin lesions persist after apparent CR.

² **E=week the last cycle of ET was started. E+144 visit is only for participants who received ET while on study and have already completed the week R+96 visit on the last step entered.**

³ **Complete only if the participant is receiving bleomycin.**

6.2 Timing of Evaluations

All evaluations will be performed following the Schedule of Events.

6.2.1 Screening Evaluations

Screening evaluations must occur prior to entry.

Screening evaluations to determine eligibility must be completed within 30 days prior to study entry unless otherwise specified in section 4.1.

Stratification will be based on the screening CD4+ lymphocyte cell count and country.

In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured in a screening failure results form and entered into the ACTG database.

6.2.2 On-Study Evaluations

6.2.2.1 Entry

Evaluations must be done prior to the participant taking any study treatment. Participants must begin treatment after randomization and within 72 hours after entry.

6.2.2.2 Post-Entry

In the interest of participant safety, evaluations required to ensure safe and timely treatment may be conducted within three days prior to administration of chemotherapy.

The results of a complete blood count and creatinine drawn no more than three days earlier must be available prior to administration of each cycle of chemotherapy.

Even if delayed, all chemotherapy cycles should be completed unless there is a dose-limiting toxicity, a study endpoint is met, or there is IERC-confirmed KS progression.

Step 1

Study visits must be scheduled on the weeks indicated in section 6.1, the SOE, ± 7 days for the baseline visit to week 48.

Study visits must be scheduled on the weeks indicated in section 6.1, the SOE, ± 14 days for the week 60 visit to week 96.

Study visits must be scheduled on the weeks indicated in section 6.1, the SOE, ± 12 weeks for the **week E+144 visit**.

Steps 2, 3, and 4

Study visits must be scheduled on the weeks indicated in the SOE ± 7 days for the step randomization visit to week R+48.

Study visits must be scheduled on the weeks indicated in the SOE, ± 14 days for the week R+60 visit to week R+96.

Study visits must be scheduled on the weeks indicated in the SOE ± 12 weeks for the E+144 visit.

6.2.2.3 Event-Driven Evaluations

6.2.2.3.1 Participants who Enter Step 2

These participants will be provided a second course of up to six additional cycles of the same chemotherapy utilized in Step 1. After Step 2 entry, the participant will follow the Step 2 SOE.

Entry into Step 2 can only occur **fewer than** 72 weeks after Step 1 entry.

6.2.2.3.2 Participants who Enter Step 3

Participants who move to Step 3 will follow the Step 3 SOE.

Entry into Step 3 can only occur **fewer than** 72 weeks after Step 1 entry.

6.2.2.3.3 Participants who Enter Step 4

Participants who enter Step 4 will follow the Step 4 SOE.

Entry into Step 4 can only occur **fewer than** 72 weeks after Step 1 entry.

6.2.2.3.4 KS-IRIS Evaluation

At the time of suspected KS-IRIS (see section 7.2.1 for the definition of suspected KS-IRIS), the assessments indicated in the SOE must be obtained if not already required for the scheduled visit.

6.2.2.3.5 Long-Term Safety Follow-Up

Participants who received ET while on study will be followed for at least 144 weeks after beginning the last cycle of ET. All other participants will be followed for 96 weeks after randomization or assignment to the last step they enter.

6.2.3 Evaluations for Randomized or Registered Participants Who Do Not Start Study Treatment (Chemotherapy and ART)

There will be no further evaluations for randomized participants who do not start study treatment. All CRFs including study entry and off-study forms must be completed and keyed.

6.2.4 Premature Treatment Discontinuation Evaluations

Participants who permanently discontinue study treatment will be asked to continue in the study in an off-study treatment/on-study status. The participant will receive all study evaluations per the participant's current Step SOE to completion of the study. No extra evaluations are required at the time of the treatment discontinuation. For treatment discontinuation due to pregnancy, see section 7.22.

6.2.5 Premature Study Discontinuation Evaluations

Participants who prematurely discontinue from the study will have the discontinuation evaluations per the SOE performed prior to being taken off the study. These evaluations should only be performed if the participant is leaving the study prior to week 48 **on Step 1 or prior to week R+48 on Steps 2, 3, or 4.**

6.3 Instructions for Evaluations

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS website for information about what must be included in the source documents:

<https://www.niaid.nih.gov/sites/default/files/documents/sourcedocappndx.pdf>

All stated evaluations are to be recorded on the CRF and keyed into the database unless otherwise specified. This includes events that meet the International **Council for Harmonization (ICH)** definitions for a serious adverse event:

- Results in death
- Life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect

- Other important medical event (may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the events listed above.

To grade diagnoses, signs and symptoms, and laboratory results, sites must refer to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004 (Clarification, August 2009), which can be found on the DAIDS RSC website: <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables>.

6.3.1 Documentation of HIV-1

Please refer to section 4.1.1 regarding assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the CRF.

6.3.2 Biopsy Diagnostic of KS (fixed in formalin)

Histologically-confirmed KS based on review by a pathologist at a DAIDS-approved pathology laboratory of a biopsy of a suspected KS lesion. If a diagnostic biopsy specimen is not available for review, it must be performed at screening. Please refer to the **A5263/AMC066** MOPS for instructions.

In participants in whom hyperpigmented macular skin lesions persist after apparent CR, biopsy of at least one representative lesion is required in order to document the absence of malignant cells.

If a diagnostic biopsy is performed as part of screening and a residual tissue block is available for further study, the remainder will be used to generate a study-specific tissue microarray (TMA). Study-specific TMAs will be used to characterize patterns of viral and cellular gene expression in relation to study outcomes as described in Appendix IV.

6.3.3 Documentation of Current KS stage T1 using ACTG criteria [29].

KS stage T1 must be documented on the CRF at screening.

KS stage T1 (ACTG criteria; [29]) is KS with any of the following:

- symptomatic tumor-associated edema
- tumor ulceration
- extensive oral KS (other than flat KS confined to the hard palate)
- gastrointestinal KS
- KS in any other non-nodal visceral organ (e.g., lung)

6.3.4 Documentation of KS Cutaneous Marker Lesions

Please refer to **the** A5263/AMC066 MOPS for detailed instructions on assessment and documentation of cutaneous marker lesions.

The presence of cutaneous marker lesions at screening does not require the completion of a CRF.

6.3.5 Medical/Medication History

Medical History

A medical history, including allergies to any medications and their formulations, will be collected. All diagnoses identified by the ACTG criteria for clinical events and other diseases must be recorded. Refer to the study CRF for the appropriate appendix used for the current ACTG criteria.

In addition to the diagnoses identified by the ACTG criteria for clinical events and other diagnoses, the medical history should include any previously diagnosed, pathologically proven malignancy, including squamous cell carcinoma of the skin and basal cell carcinoma.

Medication History

All previous ART medication and corticosteroids taken at any time prior to entry and all current medications, with start and stop dates (estimated if the exact dates cannot be obtained), should be recorded in source documents and on the CRFs. All previous use of topical and systemic steroids should be recorded on the source documents and on the CRFs.

6.3.6 Concomitant Medications

After entry and **up** to week 96, all prescription, non-prescription, alternative, and traditional concomitant medications taken since the last visit will be recorded in the source documents. Include all start and stop dates for concomitant medications.

All concomitant medications, whether or not they are prescription or nonprescription, will be recorded on the CRF. Only start and stop dates must be recorded on the CRF.

Alternative and traditional medications will be reported as Yes/No on the CRF. Vitamins DO NOT need to be recorded as alternative and traditional medications.

After week 96 (**or R+96 for participants who enter step 2, 3, or 4**), only chemotherapy or radiation should be recorded in the CRF and source documents.

6.3.7 Complete Physical Exam

A complete physical examination at screening is to include at a minimum:

- measurement of weight and height
- examination of the skin, head, mouth, and neck
- auscultation of the chest
- cardiac exam
- abdominal exam
- examination for tumor associated edema
- Karnofsky performance status. Please refer to the A5263/AMC066 MOPS for Karnofsky performance status instructions.
- signs and symptoms
- diagnoses
- vital signs (temperature, pulse, respiration rate, and blood pressure)

6.3.8 Body Surface Area Calculation

Body surface area will be calculated at study entry for participants receiving bleomycin or PTX in order to calculate the appropriate **initial** chemotherapy doses.

Body surface area may be recalculated and the appropriate chemotherapy doses recalculated at each treatment visit.

Body surface area must be recalculated and the dose of bleomycin or PTX recalculated any time the participant's weight has changed by 10% or more from the step entry measurement.

The calculator can be found under “calculators” on the Data Management Center’s website,
<https://www.fstrf.org/apps/cfm/apps/common/Portal/index.cfm>.

Body surface area should be recorded on the CRF.

6.3.9 Targeted Physical Exam

A targeted physical examination is to include weight, vital signs (temperature, pulse, respiration rate, and blood pressure), and is to be driven by any previously identified or new signs or symptoms including diagnoses that the participant has experienced since the last visit. This examination will be performed at entry and at every subsequent visit.

6.3.10 Clinical Assessments

Signs and Symptoms

At entry, all signs and symptoms of any grade that occurred within 30 days before entry must be recorded. After study entry, all grade 3 and 4 signs and symptoms must be recorded. In addition, all signs and symptoms that led to a change in treatment, regardless of grade, must be recorded.

If an expedited adverse event (EAE) or pregnancy occurs between scheduled visits, complete and key all CRFs related to that EAE or pregnancy at the time the EAE is reported or the pregnancy is determined.

Diagnoses

Report diagnoses identified by the ACTG Criteria for Clinical Events and Other Events at study entry and since the last visit. Refer to the study CRF for the appropriate appendix used for the current ACTG criteria.

All related signs, symptoms, laboratory results, or diagnostic test results observed or performed as part of establishing a diagnosis are also reportable on the CRF, regardless of grade.

The following diagnoses: death, malignancy, AIDS-defining illnesses, or severe/life-threatening events will be recorded on the CRF. Please refer to section 11.4 for SAE event reporting.

Study Treatment Modifications, ART

All modifications to ART including initial doses, participant-initiated and/or protocol-mandated interruptions, modifications, and permanent discontinuation of ART will be recorded. Participant-initiated and protocol-mandated interruptions include both inadvertent and deliberate interruptions of any ART. Treatment interruption is failure for any cause to take ART for more than 48 hours.

Study Treatment Modifications, Chemotherapy

All modifications to chemotherapy including initial doses, participant-initiated and/or protocol-mandated interruptions, modifications, and permanent discontinuations will be recorded. Participant-initiated and protocol-mandated interruptions include both inadvertent and deliberate interruptions of any chemotherapy.

If a study participant is identified by the site as having progressive KS, **using the definitions in section 7.0, the site must have the KS progression confirmed by the IERC in order to change the participant's chemotherapy.** Details and requirements for this request can be found in the **A5263/AMC066** MOPS.

6.3.11 KS Exam

The KS exam will be performed according to the section 6.1. The entry KS tumor assessment must be conducted prior to receiving study medication but may be performed no earlier than 2 weeks before initiating treatment. Please refer to the A5263/AMC066 MOPS for instructions on KS exam.

If a participant begins a new chemotherapy regimen, a new baseline tumor assessment must be performed within 7 days prior to initiating the new therapy.

All subsequent assessments of KS response to new chemotherapy and decisions about discontinuation of therapy for KS progression will be made with respect to the new baseline.

6.3.12 Photographic Record

Photographs will be taken to assist in documentation of diagnosis of KS and for clinical monitoring purposes. Photographic documentation of KS progression is required. This documentation will not be collected on the CRF. Please refer to the A5263/AMC066 MOPS for instructions.

6.3.13 KS Tumor Punch Biopsy for Storage in RNA later

KS tumor punch biopsies will be performed according to the SOE. Please refer to the A5263/AMC066 MOPS for detailed instructions on tumor biopsy procedures. Lesions used as cutaneous marker lesions for measuring response to treatment should NOT be the lesions chosen for biopsies for Tumor Marker Assessments.

If safe and feasible, KS tumor punch biopsies must be obtained when KS-IRIS is suspected.

KS tumor punch biopsies are strongly encouraged in Step 2, Step 3, and Step 4.

KSHV transcriptional virus profiling will be completed on these KS tumor punch biopsies as described in Appendix V.

6.3.14 CD4+/CD8+

Absolute CD4+ lymphocyte cell counts and percentages will be obtained from a DAIDS-approved laboratory at screening and throughout the study. CD8+ lymphocyte cell counts and percentages are also required if they are measured in a DAIDS-approved laboratory as part of the CD4+ lymphocyte cell count measurement. All results will be recorded in the source documents and on the CRFs and should be obtained from the same laboratory, if possible.

During the study, all laboratories must be certified for protocol testing by the DAIDS Immunology Quality Assurance (IQA) Program.

6.3.15 Plasma HIV-1 RNA

HIV-1 RNA must be performed by a laboratory certified by the DAIDS Virology Quality Assurance (VQA) Program. HIV-1 RNA data will be reported on the CRF when they are not reported through the Laboratory Data Management System (LDMS).

6.3.16 Stored Serum, Plasma, and PBMC for Protocol-Related Research

Serum, plasma, and PBMC will be collected and stored according to the SOE.

Plasma and PBMC will be collected and stored for KSHV viral load assays.

Serum will be collected and stored for measuring levels of cytokines and inflammation- and angiogenesis-associated molecules as outlined in Appendix II.

PBMCs will be collected and stored for ELISPOT and polyfunctional intracellular cytokine staining (ICS) as outlined in Appendix III.

Please refer to the A5263/AMC006 MOPS and laboratory processing chart (LPC) for additional information on sample collection.

6.3.17 Laboratory Evaluations

At screening and entry all laboratory values must be recorded. For post-entry assessments, record all Grade ≥ 2 laboratory values. All laboratory toxicities that led to a change in treatment, regardless of grade, must be recorded.

Hematology

Hemoglobin, hematocrit, white blood cell count (WBC) with differential, ANC, and platelets required.

Chemistries

Sodium, potassium, chloride, CO₂, phosphate, glucose, creatinine, albumin, AST, ALT, alkaline phosphatase, and total bilirubin.

Calculated creatinine clearance will be used to determine study eligibility and to dose adjust renally excreted ART medication. Please refer to the A5263/AMC006 MOPS for calculation procedure. The calculated creatinine clearance results should be recorded on the CRF after entry regardless of grade.

Hepatitis B Surface Antigen

HbsAg reactivity will be determined at study entry.

Lactate

Lactate is recommended for evaluation of participants with suspected lactic acidosis. Please refer to the A5263/AMC006 MOPS for lactate collection and storage guidelines.

Lipase and Triglycerides

Lipase and triglycerides will be measured whenever needed for evaluation of suspected pancreatitis. A triglyceride level should be drawn with the lipase, whether fasting or not. Pancreatic amylase is also acceptable. If a baseline measurement is needed, it will be obtained from stored samples.

Creatinine Kinase

Measure creatinine kinase whenever needed for evaluation of suspected myopathy.

Urinalysis

Urine reagent strip will be performed. Results will be recorded on the CRF. If abnormalities greater than trace are found, a specimen for complete urinalysis must be done at the local laboratory.

Pregnancy Testing

Study participants of reproductive potential (defined in 4.1.7) must have a negative β -HCG serum or urine pregnancy test within 48 hours prior to starting study treatment and at every visit prior to a new chemotherapy cycle. The urine test must have a sensitivity of 15-25 mIU/mL.

All pregnancy test results must be recorded. Obtain a pregnancy test at any other time pregnancy is suspected.

If a participant becomes pregnant after study entry, she may elect to continue on study but off study-provided chemotherapy. If a participant becomes pregnant, refer to section 7.22 for clinical management details. If pregnancy occurs between scheduled visits, complete and key all CRFs related to that pregnancy at the time the pregnancy is determined. If the participant elects to continue on study, pregnancy-related information will be reported on a CRF and she will not have pregnancy tests at her follow-up visits.

6.3.18 CXR

A **CXR** will be conducted and read locally at screening to assess the presence of pulmonary KS and will be repeated at the time of suspected or IERC-confirmed KS progression and/or entry into an additional step.

For participants with known pulmonary KS at study entry or at the time of entry into the next step, a **CXR** will be repeated every third cycle.

When available, and if clinically indicated, CXRs may be supplemented by CT scans to better define the presence of pulmonary KS, its extent, and its response to treatment.

6.3.19 Pulse Oximetry

Pulse oximetry will be conducted at rest and **after exercise**.

NOTE: Rest is defined as sitting for 5 minutes.

NOTE: Exercise is defined as any activity that will increase a participant's resting heart rate by 20 beats/minute.

6.3.20 Peripheral Neuropathy Assessment

Neuropathy Assessment

Neuropathy assessments will be performed as indicated in the SOE. Neuropathy assessments should be performed by the same site personnel at each evaluation, **if possible**. The A5263/AMC066 team recommends that neuropathy assessments be performed by a physician investigator, but this is not a requirement, and neuropathy assessments may be performed by **trained** non-physician site investigators **or site personnel**. To ensure that the neuropathy assessments are performed consistently across different sites, all study personnel assigned to complete the neuropathy exams must receive appropriate training. Relevant neuropathy training material will be available on the A5263/AMC066 PSWP. Detailed instructions will also be on the A5263/AMC066 neuropathy examination CRF.

For a detailed case definition of neuropathy as well as a case definition for chemotherapy-associated toxic neuropathy, refer to the A5263/AMC066 MOPS.

Final determination of a neuropathy diagnosis that requires modification of study treatment must be confirmed by the site investigator.

Brief Peripheral Neuropathy Screening (BPNS)

The BPNS will be completed as part of the neuropathy assessment. The BPNS is a validated PN screening tool [60,61] which assesses common PN symptoms and signs. Common PN symptoms (pain, numbness, paresthesias or 'pins and needles' sensations) are documented on a numerical rating scale graded from 0 to 10. Vibratory sensation at the distal interphalangeal joint of the great toe with a 128 Hz tuning fork and lower extremity reflexes constitute the focused neuromuscular examination.

NOTE: PN severity grades will be determined by the BPNS symptom severity score rather than the DAIDS AE Grading table.

6.3.21 ART Adherence Assessment

Trained site personnel will conduct the adherence assessment. Trained site personnel are defined as site pharmacist, nursing staff, clinician, or other trained clinical personnel (e.g., adherence counselors, social workers).

See the CRF for specific instructions.

6.3.22 ET Adherence Assessment

Initiation of ET in all steps was discontinued as of March, 2016. The following instructions are provided for participants currently receiving ET in any step who elect to complete their current course of ET:

Trained site personnel will conduct the adherence assessment. Trained site personnel are defined as site pharmacist, nursing staff, clinician, or other trained clinical personnel (e.g., adherence counselors, social workers).

See the CRF for specific instructions.

6.3.23 Quality of Life Assessments

Trained site personnel will administer the **Quality of Life** questionnaire and Clinical Benefit form and record results on the CRFs. Trained site personnel are defined as site pharmacist, nursing staff, clinician, or other trained clinical personnel (e.g., adherence counselors, social workers). It is estimated that this assessment will take 10-15 minutes to complete. See the CRFs for specific instructions.

7.0 CLINICAL MANAGEMENT ISSUES

ANTIRETROVIRAL AND CHEMOTHERAPY MANAGEMENT: TOXICITIES, DRUG SUBSTITUTIONS, PREGNANCY, OPPORTUNISTIC INFECTIONS, AND OTHER CONDITIONS

This section provides guidelines for management of toxicities related to chemotherapy and commonly used ART that may be provided either through A5263/AMC066 or obtained outside of the study. When one ART is held for resolution of toxicity, all ART in the regimen should be held concurrently unless otherwise specified.

Every attempt should be made to continue to follow participants who discontinue study treatment because of a Grade 3 or 4 AE until resolution of the AE can be documented.

Toxicity management may require reliance on clinical symptoms, clinician judgment, and available laboratory markers, since alternatives to study-provided ART may be very limited and baseline levels of certain laboratory parameters (e.g., hemoglobin) may be different than in other settings. The CMC is available to discuss toxicity management of both study and non-study ART with investigators. Sites must contact the CMC to request permission to make any changes in ART and chemotherapy.

It is recommended that NRTIs be continued for 7 days past NNRTI (e.g., EFV, NVP) discontinuation unless they are suspected in a given toxicity. If available, a PI/r may be substituted for the 7 days that the NNRTI has been discontinued and then also stopped when the NRTIs are discontinued at the discretion of the site investigator.

FTC and TDF may have activity against hepatitis B virus (HBV). Permanent discontinuation of FTC or TDF may result in re-activation of HBV. Participants who discontinue FTC and/or TDF should be followed carefully for up to 16 weeks to monitor for a flare of HBV, according to local standard of care.

A5263/AMC066 will use the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification August 2009), as a guideline for grading toxicities related to study drugs unless otherwise noted. The table is located at the RSC website: <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables>.

Except where noted below, study-prescribed chemotherapy should be held if a Grade ≥ 3 AE develops that is considered to be related to the chemotherapeutic agent. Treatment may resume when the toxicity improves to Grade ≤ 1 .

If necessary for medical or administrative reasons (e.g., adverse event, intercurrent illness, missed appointment), the start of a new treatment cycle may be delayed for up to 42 days after the first day of the previous cycle. If a new treatment cycle is delayed more than 42 days after the start of the previous cycle for any reason, study-provided chemotherapy should be discontinued.

7.1 KS Response

Please refer to the A5263/AMC066 MOPS for detailed information on calculating response categories and for the definition and instructions on evaluating non-measurable (evaluable) disease.

For purposes of this study, IERC-confirmed KS progression is defined as KS progression that has been verified by the IERC. It is required that all KS progression be confirmed by the IERC. Changes in chemotherapy cannot occur until the site has received confirmation from the IERC. Please refer to the A5263/AMC066 MOPS for detailed instructions on contacting the IERC.

Once a participant has shown an objective **CR or PR**, subsequent assessments of KS progression will be made with respect to the “best response”. In participants who have shown an objective, measured response, subsequent progression will be assessed with respect to the smallest measurements recorded since the treatment started using the criteria in sections 7.1.1-7.1.4 (for measurable cutaneous disease) and 7.1.5 (for non-cutaneous disease).

7.1.1 Complete Response (CR)

CR is defined as the absence of any detectable residual disease, including tumor-associated edema, persisting for at least 4 weeks. In some individuals, residual skin color changes may remain visible at one or more site(s) of lesions

that were previously raised and/or red or violaceous. Suspected CR in those lesions refers only to residual macules (flat, non-palpable lesions) that are slightly darker than the surrounding normal skin. In the event such lesions are present in a participant otherwise believed to have a CR, biopsy of at least one such lesion is required in order to document the absence of malignant cells and to confirm CR. In the event that such a confirmatory biopsy is not performed and residual pigment persists, the response will be considered partial (PR). In participants in whom all detectable cutaneous disease has resolved and in whom there are no visible pigmented macules as described above, a confirmatory skin biopsy is not required. In participants known to have had visceral disease, an attempt at restaging with appropriate endoscopic or radiographic procedures should be made.

NOTE: To classify a response as a CR, the participant must have a CR in both the cutaneous and noncutaneous (if applicable) sites of disease and no evidence of progression as defined by the above criteria.

7.1.2 Partial Response (PR)

PR is defined as no new oral lesions or new or progressive visceral sites of involvement, or the appearance or worsening of tumor-associated edema (as defined in section 8 of the **A5263/AMC066** MOPS) or effusions or the development of five or more new cutaneous lesions in anatomic sites which were previously documented as having no evidence of cutaneous disease; AND

- A 50% or greater decrease in the number of all lesions present at entry (either total body or in the representative areas) lasting for at least 4 weeks; OR
- Complete flattening of at least 50% of all previously raised lesions (i.e., 50% of all nodular or plaque-like lesions become macules, either total body or in the representative areas) present at entry **lasting for at least 4 weeks**; OR
- A 50% **or greater** decrease in the area of the cutaneous marker lesions compared **with** entry **lasting for at least 4 weeks**; OR
- **A 50% or greater decrease in the number or size of all measurable oral or visceral lesions lasting for at least 4 weeks, without evidence for progression of cutaneous lesions**; OR
- **Complete disappearance of non-measurable oral or visceral lesions lasting for at least 4 weeks, without evidence for progression of cutaneous lesions.**

NOTE: To classify a response as PR, the participant must have at least a PR in either the cutaneous or noncutaneous sites of disease and no evidence of progression as defined in the above criteria.

NOTE: Participants with residual tumor-associated edema or effusion who otherwise meet the criteria for CR will be classified as having a PR.

7.1.3 Stable Disease

Stable disease is defined as any response not meeting the criteria for CR, PR, or progressive disease.

7.1.4 Progressive Disease (PD)

For participants with ≤ 50 cutaneous lesions

PD is defined as any one or more of the following:

- $\geq 25\%$ increase in the area of the cutaneous marker lesions compared to entry or best response;
- $\geq 25\%$ increase in the total lesion count, or a minimum of five new lesions, **whichever is greater**, compared **with** entry or best response;
- $\geq 25\%$ increase in the number of raised lesions, **or a** minimum of five new raised lesions, **whichever is greater**, compared **with** entry or best response.

NOTE: There are body sites where disease is particularly difficult to evaluate, and a few new lesions may be counted in spite of the fact that a participant is not actually progressing. For example, lesions of the foot, particularly those that are flat, are difficult to evaluate because their intensity may vary based on how much edema is present, how much the person walked the day before, how long his/her feet have been in a dependent position prior to the physical exam.

For participants with > 50 cutaneous lesions

PD is defined as any one or more of the following:

- $\geq 25\%$ increase in the area of the cutaneous marker lesions compared to entry or best response;
- $\geq 25\%$ increase in the total number of lesions in the prospectively defined anatomic sites containing representative lesions;
- a total of five new lesions in anatomic sites that were previously documented as having no evidence of cutaneous disease,
- $\geq 25\%$ increase in the number of raised lesions in the prospectively defined anatomic sites containing representative lesions (minimum of five raised lesions if there are very few raised lesions, for example < 8) whichever is greater. Photographic documentation of "gross" or significant progression, particularly in areas that were not being followed, will be of particular value.

7.1.5 Noncutaneous PD

Noncutaneous PD includes new oral or visceral sites of involvement or progression of oral or visceral disease or the development of new or increasing tumor-associated edema or effusion that interferes with the participant's normal activities lasting for at least two consecutive evaluations. Progressive oral or visceral disease, for measurable and evaluable disease, should be analogous to cutaneous KS response criteria.

Progressive edema is defined as the following:

- an increase in non-pitting/woody edema in an upper or lower extremity associated with an increase in limb circumference of at least 3 cm from entry or best response, sustained for at least two consecutive evaluations, and measured at a fixed point on the extremity with respect to a bony landmark (e.g., 10 cm below the lower border of the patella); AND/OR
- new appearance of non-pitting/woody edema in an extremity where none was previously present, sustained for at least two consecutive evaluations; AND/OR
- new or worsening edema in a non-extremity site (e.g., periorbital, genital) that interferes with function and is sustained for at least two consecutive evaluations.

7.2 IRIS Management

7.2.1 KS-IRIS

For purposes of this study, a suspected case of KS-IRIS is defined as any progression of KS, as defined above, that occurs within 12 weeks of initiation of ART that is associated with an increase in CD4+ count of at least 50 cells/ μ L above the study entry value and/or a decrease in the HIV RNA level by at least 0.5 log below the study entry value prior to, or at the time of documented KS progression.

Participants who develop symptoms consistent with KS-IRIS during the study should have the evaluations listed in the KS-IRIS column of the SOE, as soon as possible after presentation.

When KS-associated IRIS is suspected, the CMC should be consulted. This syndrome should be considered for all worsening of KS lesions within the first 12 weeks of ART. Worsening may include enlargement of existing lesions, development of new skin lesions, or edema, or the development of signs/symptoms suggestive of new visceral disease. See the SOE for procedures to be conducted.

The following management plan should be followed:

- Continue ART
- Evaluate for alternative opportunistic infections to explain the syndrome
- Continue chemotherapy, if participant is currently receiving chemotherapy
- Any modification or initiation of chemotherapy because of disease progression requires confirmation of disease progression by the IERC.
- Initiate anti-inflammatory agents, such as non-steroid agents at the discretion of the site investigator.

The use of corticosteroids for KS-IRIS management is left to the discretion of the site investigator. However, corticosteroid use should be avoided whenever possible.

If there is a case of suspected KS-IRIS and KS progression that persisted or worsened after 2 weeks of non-steroid agents or other interventions, the participant should be moved to an alternative chemotherapy regimen on the next study step.

KS-IRIS events should be recorded in the CRFs, however, no EAE reporting is required, unless events are considered serious.

7.2.2 Non-KS IRIS

IRIS events are not caused by a specific or individual drug, but rather are the result of being on a successful ART treatment regimen. Management of events judged by the site investigator to be non-KS IRIS may be managed at the discretion of the site investigator.

The use of corticosteroids for non-KS IRIS management is left to the discretion of the site investigator. However, corticosteroid use should be avoided whenever possible.

Non-KS IRIS events should be recorded in the CRFs; however, no EAE reporting is required, unless events are considered serious.

7.3 Toxicity

Except as noted below, if an adverse event requiring a delay in chemotherapy does not recover to the level required for continued chemotherapy treatment within 3 weeks of the scheduled date of the next cycle (i.e., within 42 days after the start of the previous cycle), study chemotherapy should be discontinued.

In any case in which the dose of study-prescribed chemotherapy is reduced due to toxicity, any future dosing (for that cycle and all subsequent cycles) should be at the reduced dose.

7.3.1 Grade 1 or 2 Toxicity

Participants who develop a Grade 1 or 2 AE or toxicity may continue study drugs without alteration of the dosage except as stated in sections 7.4-7.22, Specific Management of Laboratory Abnormalities and Clinical Syndromes. Participants experiencing Grade 1 or 2 toxicities will be managed at the discretion of the site investigator.

7.3.2 Grade 3 Toxicity

If there is compelling evidence that the AE has NOT been caused by the study drugs, dosing may continue. Except as stated above, participants who develop a Grade 3 AE or toxicity thought secondary to study medications or of unknown

etiology may have all of their study drugs withheld at the site investigator's discretion. Dose reductions are not permitted.

Investigators are encouraged to discuss toxicity management with the CMC. The participant should be re-evaluated weekly if possible until the AE returns to Grade ≤ 2 , at which time the study drugs may be reintroduced at the discretion of the site investigator.

7.3.3 Grade 4 Toxicity

Participants who develop a symptomatic Grade 4 AE or toxicity, not specifically addressed below, will have all study drugs withheld until resolution of the AE to a Grade ≤ 2 . Under certain circumstances the study drug thought most likely to be related to the AE may be resumed at the discretion of the site investigator after discussion with the CMC. Alternative study-provided or non-study-provided drugs should be considered.

Participants with Grade 4 asymptomatic laboratory abnormalities, not specifically addressed below, may continue study drug therapy if the site investigator has compelling evidence that the toxicity is NOT related to the study drugs, or if benefit of the study drugs outweighs the potential risk.

7.4 Anemia/Neutropenia/Thrombocytopenia

Clinicians should be alert to clinical signs of anemia, neutropenia and thrombocytopenia and participants should receive education or counseling about the associated symptoms. Participants who develop anemia, neutropenia, and/or thrombocytopenia on study should be evaluated for causes of anemia and/or neutropenia, such as concurrent bacterial, mycobacterial or fungal infection, malaria, helminthiasis, malignancy and/or malnutrition. Transfusion or treatment with recombinant G-CSF or recombinant erythropoietin should be considered if clinically appropriate and available at the site.

7.4.1 Anemia

NOTE: Management rules assume that erythropoietin will NOT be available.

For hemoglobin ≥ 8.0 , no dose modification for any chemotherapeutic agent is required. Transfusion is not required.

For any hemoglobin < 10.0 , if the participant is receiving ZDV, stopping ZDV and switching to another NRTI, where available, is recommended.

For hemoglobin $< 8.0 - 6.5$, red blood cell transfusion is recommended to increase the hemoglobin level to ≥ 8.0 . Chemotherapy can continue for hemoglobin $< 8.0 - 6.5$.

For hemoglobin <6.5, chemotherapy should be held and the participant transfused with red blood cells until the hemoglobin level has returned to ≥ 8.0 . Study medication may then be resumed at full dose.

If hemoglobin <6.5 recurs after resumption of chemotherapy, the participant should again be transfused as above. Chemotherapy may then be resumed as follows:

- Participants receiving PTX: 25% dose reduction
- Participants receiving BV: 25% reduction in the dose of both drugs
- Participants receiving ET: If the participant's dose has already been escalated from the starting dose, then resume dosing at the next lowest dose level. If the participant's dose has not been escalated above the initial dose (50 mg BID for 7 days), then reduce duration of dosing on the next cycle from 7 days to 4 days.

7.4.2 Neutropenia

NOTE: Management rules assume that G-CSF will NOT be available.

For any grade neutropenia, if the participant is receiving ZDV, stopping ZDV and switching to another NRTI, where available, is recommended.

For any ANC ≥ 1000 , no modification in chemotherapy doses is required.

For ANC <1000 at the beginning of any scheduled treatment cycle, chemotherapy will be withheld until the ANC is ≥ 1000 . Chemotherapy may then be resumed as follows:

- Participants receiving PTX: 25% dose reduction
- Participants receiving BV: 25% reduction in the dose of vincristine only, no reduction in bleomycin
- Participants receiving ET: If the participant's dose has already been escalated from the starting dose (50 mg BID for 7 days), then resume dosing at the next lowest dose level. If the participant's dose has not been escalated above the initial dose, then reduce duration of dosing on the next cycle from 7 days to 4 days.

If the neutrophil count does not recover to the level required for continued chemotherapy treatment within 3 weeks, study chemotherapy will be discontinued.

If ANC <1000 recurs after the first chemotherapy drug dose reduction, chemotherapy should again be withheld until the ANC is ≥ 1000 . A second dose reduction may be instituted as follows:

- Participants receiving PTX: 50% reduction from the original dose.
- Participants receiving BV: Discontinue BV.

- Participants receiving ET: Reduce the dose to the next lowest dose level. If the study participant is already on the lowest dose level (i.e., 4 days only at 100 mg per day), ET will be discontinued.

7.4.3 Thrombocytopenia

For platelets $\geq 50,000$, no change in the dose of any chemotherapeutic agent is required.

For platelets $< 50,000$, chemotherapeutic agents will be held until the platelet count increases to $\geq 50,000$. Chemotherapy may then be resumed as follows:

- Participants receiving PTX: 25% dose reduction
- Participants receiving BV: 50% reduction in the dose of vincristine only, no reduction in bleomycin
- Participants receiving ET: If the participant's dose has already been escalated from the starting dose, then resume dosing at the next lowest dose level. If the participant's dose has not been escalated above the initial dose (50 mg BID for 7 days), then reduce duration of dosing on the next cycle from 7 days to 4 days.

If the platelet count again falls to $< 50,000$ after dose reduction of vincristine or ET, chemotherapy will be discontinued.

If the platelet count again falls to $< 50,000$ after the first dose reduction of PTX, PTX will be held until the platelet count increases to $\geq 50,000$. PTX treatment may then be resumed at a 50% reduction from the original dose.

If the platelet count again falls to $< 50,000$ after the second dose reduction of PTX, PTX chemotherapy will be discontinued.

7.5 Peripheral Neuropathy (PN)

[After entry, for participants receiving vincristine or PTX only]

NOTE: PN severity grades will be determined by the BPNS symptom severity score rather than the DAIDS AE Grading table.

For Grade 1-2 symptomatic PN, BV or PTX may be continued. Treatment of neuropathy symptoms may be offered as available in line with local standard of care. If a participant is receiving an ART drug associated with PN, stopping that particular drug and switching to an alternative NRTI is recommended, where available.

For Grade ≥ 3 PN when on BV, BV will be permanently discontinued. Symptomatic treatments to treat neuropathy symptoms may be offered as available in line with local standard of care.

For Grade ≥ 3 PN when on PTX, PTX treatment should be held for a maximum of 3 weeks. If PN has not recovered to grade 1 or less within 3 weeks, PTX will be permanently discontinued. If Grade ≥ 3 PN has recovered to Grade 1 or less within 3 weeks, PTX should be reduced by 25%. Recurrence of ≥ 3 PN after dose reduction will require permanent discontinuation of PTX.

7.6 Hyperbilirubinemia

NOTE: Grading of hyperbilirubinemia does not apply to participants who are receiving atazanavir (**ATV**).

For Grade 1 hyperbilirubinemia, no change in the dose of any chemotherapeutic agent is required.

For Grade 2 hyperbilirubinemia, the dose of chemotherapeutic agents will be modified as follows:

- Participants receiving PTX: 50% dose reduction
- Participants receiving BV: Discontinue BV.
- Participants receiving ET: If the participant's dose has already been escalated from the starting dose, then resume dosing at the next lowest dose level. If the participant's dose has not been escalated above the initial dose, then reduce duration of dosing on the next cycle from 7 days to 4 days.

If Grade 2 hyperbilirubinemia recurs after modification of the dose of PTX or ET, or if Grade 3 or 4 hyperbilirubinemia occurs at any time, chemotherapy will be discontinued, except as noted below.

For isolated Grade >3 unconjugated hyperbilirubinemia attributed to **ATV**, **ATV** should be continued unless associated with jaundice or scleral icterus that presents an intolerable cosmetic concern to the participant.

For Grade >3 that cannot be attributed to **ATV** or a non-study drug related cause, all study medications should be held pending evaluation of etiology.

7.7 Lipase Elevations and Pancreatitis

Pancreatitis will be reported as a clinical finding (i.e., symptomatic pancreatitis). The primary enzyme abnormality used for making the diagnosis is the lipase level. When obtained, lipase determinations will be recorded in the CRF. A triglyceride level should be drawn with the lipase.

Lipase will be obtained for participants if development of clinical symptoms suggests pancreatitis. If a baseline measurement is needed, it will be performed from stored entry samples. (Pancreatic amylase is also acceptable.)

For symptomatic gastrointestinal symptoms (particularly abdominal pain) with elevations in lipase:

- Grade 1: Search for other causes of symptoms. If none is found and symptoms persist, repeat lipase within 2 weeks.
- Grade ≥ 2 : Follow participants and repeat lipase as soon as possible. If lipase is persistently elevated and accompanied by symptoms, then participants should be considered to have clinical pancreatitis. CT scan of the abdomen, if available, may also be helpful in determining whether clinical pancreatitis is present. Exclude other possible diagnoses (e.g., renal insufficiency causing false elevations in lipase). If none is found, diagnose as clinical pancreatitis.

For a diagnosis of pancreatitis (clinical), ALL study medications should be held. After complete resolution of the episode in a setting in which other concomitant illness might have reasonably contributed to the development of pancreatitis, rechallenge with study medications may be performed in consultation with the CMC.

Upon rechallenge, lipase determinations should be performed monthly. Any elevation of lipase of Grade ≥ 2 or any recurrence of symptoms during this period will lead to a reevaluation and permanent discontinuation of the suspected study drugs.

7.8 AST and ALT Elevation

Nearly all the study drugs, isoniazid (INH), and concomitant illness can cause alterations in **liver function tests (LFTs)**. Therefore, changes in AST or ALT should be evaluated within the clinical context of the participant. Initiation of treatment and INH has been staggered to facilitate the interpretation of LFTs. Because INH and the NNRTIs have been most associated with serious, life-threatening hepatitis, evaluation of LFTs in the setting of these drugs is discussed separately.

General Considerations: For asymptomatic elevation in AST or ALT of 5-10 \times ULN (Grade 3), medications other than NNRTIs and INH may be continued at the discretion of the site investigator. Careful assessments should be done to rule out alcohol use, non-study medication-related drug toxicity, the lactic acidosis syndrome, and viral hepatitis as the cause of the transaminase elevation. If the AST/ALT elevation is considered most likely to be due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent, should be undertaken.

For asymptomatic elevation 5-10 \times ULN (Grade 3) believed secondary to study medications, all agents must be held until levels are Grade ≤ 2 , at which time therapy may be reintroduced with the substitution of a PI for EFV or NVP, if applicable.

For asymptomatic or symptomatic elevation of AST or ALT $>10\times$ ULN (Grade 4), all medications must be discontinued and held until levels are Grade ≤ 2 , at which time therapy may be reintroduced with the substitution of a PI for EFV or NVP, if applicable. All medications may be restarted if the laboratory abnormalities were thought secondary to a concomitant illness. If the participant was receiving an NNRTI (EFV or NVP), either

of these medications should be considered the most likely cause of the elevations. Substitutions should be made, and the NRTI medications can be resumed. If elevations $>10\times\text{ULN}$ (Grade 4) recur in the absence of an NNRTI drug, all current treatment and INH (if participant is receiving INH) must be discontinued. Alternative treatment and TB prophylactic regimens may be considered, at the discretion of the site investigator.

INH Prophylaxis: Participants will not start INH if AST/ALT are $>3\times\text{ULN}$. At one month following initiation of INH, if AST/ALT are >3 times the baseline value, INH will be discontinued. In the event of AST or ALT $>5\times\text{ULN}$ (Grade ≥ 3) at any point thereafter, INH should be discontinued.

Clinical (Symptomatic) Hepatitis with NVP or EFV: Participants taking EFV or NVP should be monitored for the development of signs and symptoms of hepatitis, which may include fatigue, malaise, anorexia, nausea, acholic stools, bilirubinuria, jaundice, liver tenderness, or hepatomegaly, with or without initially abnormal serum transaminase levels. Anyone with these signs and symptoms must seek medical attention immediately and have LFTs performed. If the study clinician determines that the participant has clinical hepatitis with or without LFT abnormality or regardless of the degree of LFT abnormality, and NVP cannot be excluded as the cause, NVP should be permanently discontinued and not restarted after recovery. For asymptomatic elevation in AST or ALT $>5\times\text{ULN}$ (Grade ≥ 3), NVP should be discontinued.

HBV or HCV Coinfection: At study entry, hepatitis B surface antigen (HBsAg) will be obtained to facilitate management of HBV-coinfected participants in the event FTC, or TDF need to be discontinued, which would potentially worsen HBV disease.

For isolated Grade ≥ 3 unconjugated hyperbilirubinemia attributed to **ATV**, **ATV** should be continued unless associated with jaundice or scleral icterus that presents an intolerable cosmetic concern to the participant. For Grade ≥ 3 that cannot be attributed to **ATV** or a non-study drug-related cause, all study medications should be held pending evaluation of etiology.

7.9 Myopathy

CK measurements will not be performed routinely as part of the protocol. CK will be measured only if participants develop clinical symptoms consistent with a diagnosis of myopathy. If a baseline measurement is needed, it will be performed from stored samples.

For persistent CK elevations >3000 mg/dL (about $20\times\text{ULN}$) in symptomatic participants (before treatment modifications are made) CK should be redrawn after participants abstain from exercise for 24 hours. If CK is still >3000 mg/dL and the participant is receiving ZDV, ZDV should be discontinued and replaced with another NRTI as appropriate.

7.10 Lactic Acidosis

The following definition will be used.

Symptomatic Hyperlactatemia

New, otherwise unexplained and persistent (≥ 2 weeks) occurrence of one or more of the following symptoms:

- Nausea and vomiting
- Abdominal pain or gastric discomfort
- Abdominal distention
- Increased LFTs
- Unexplained fatigue
- Dyspnea

And

Lactate level (if available) $> 2 \times \text{ULN}$ confirmed by repeat lactate level analysis. In the absence of lactate levels, serum bicarbonate levels and anion gap should be assessed. The presence of depressed bicarbonate levels or an increased anion gap would suggest the possibility of lactic acidosis.

All lactates $> 2 \times \text{ULN}$ should be repeated as soon as possible, generally within 1 week. If the second result confirms hyperlactatemia ($> 2 \times \text{ULN}$), participants should immediately discontinue their current study regimen, both chemotherapy and ART.

7.11 CNS Symptoms with EFV

There have been reports of delusions and inappropriate behavior, predominantly in individuals with a history of mental illness or substance abuse. Severe acute depression has also been infrequently reported in both EFV-treated and control-treated individuals. Discontinuation of EFV may be required and substitution of NVP implemented.

7.12 Diarrhea

Diarrhea can be caused by both infection and medication toxicity. If no infectious cause of diarrhea is found and onset is temporally related to new medication, symptomatic management with antidiarrheal agents is appropriate.

7.13 Hypophosphatemia

For Grades 1 and 2 hypophosphatemia, phosphate should be repeated as soon as possible (within two weeks is optimal), and TDF may be continued if there are no other signs of renal tubular acidosis at the discretion of the site investigator. Please refer to the **A5263/AMC066** MOPS for instructions.

For Grades 3 and 4 hypophosphatemia, the phosphate should be repeated, preferably within one week. Supplemental phosphate or foods high in phosphates should be given

and other causes of low phosphate should be investigated. If Grade 3 or 4 hypophosphatemia persists discontinue TDF permanently.

7.14 Renal Insufficiency

Dose modifications are recommended for TDF, FTC, ddI-EC, d4T, and 3TC in participants with reduced creatinine clearance (see the most recent package inserts). TDF should be held for a confirmed calculated creatinine clearance <50 mL/min until an underlying etiology for the renal insufficiency is determined. If no other etiology is determined or the renal insufficiency improves with holding TDF, permanently stop TDF and substitute an alternative ARV.

Dose modifications are recommended for bleomycin and ET in participants with reduced creatinine clearance. A 25% reduction in bleomycin dose is recommended if the calculated creatinine clearance is between 15 and 50 mL/min, and a 50% reduction is recommended if the calculated creatinine clearance is below 15 mL/min. For ET, the dose will be reduced to the previous tolerated ET dose. If the participant is already at the lowest dose of ET, the ET should be discontinued.

Baseline serum creatinine will be the mean of the screening and entry values. If at any time serum creatinine is increased >1.5-fold above baseline, the serum creatinine should be repeated as soon as possible (preferably within 1 week). Participants with confirmed serum creatinine increases >1.5-fold above baseline should undergo an evaluation for potential causes of decreased renal function. Participants with confirmed increased serum creatinine >1.5-fold above baseline should have serum creatinine monitored more frequently, at the discretion of the site investigator, until serum creatinine either stabilizes or decreases to ≤1.5-fold above baseline. Drug dosing adjustments should be done based on the calculated creatinine clearance. Please refer to the A5263/AMC066 MOPS.

7.15 Cardiac Toxicity (PTX)

No treatment is required for asymptomatic bradycardia.

The PTX infusion should be stopped for symptomatic arrhythmias and the arrhythmia should be managed according to standard practice. **Permanently discontinue PTX for symptomatic cardiac events.**

The PTX infusion should also be stopped if the participant develops any chest pain and/or symptomatic hypotension (<90/60 mm Hg and requires fluid replacement). An ECG should be performed and intravenous diphenhydramine and dexamethasone, or other appropriate therapy as per institutional guidelines, should be administered if hypersensitivity is considered. Bronchodilators may be used if chest pain is not considered cardiac. PTX will be permanently discontinued for symptomatic cardiac events.

7.16 Pulmonary Toxicity

Participants receiving bleomycin who develop Grade ≥ 3 pulmonary toxicity (other than reversible toxicity attributed to intercurrent infection) will have BV permanently discontinued.

If a greater than 4% decrease in oxygen saturation develops or persists after treatment of an intercurrent infection, such as PCP, then BV will be permanently discontinued.

7.17 Management of Active Tuberculosis (TB) or Cryptococcal Meningitis (CM)

The management of active tuberculosis (TB) or cryptococcal meningitis (CM) for participants in A5263/AMC066 will be per the local standard of care at the respective sites where the study is being carried out. In cases where a participant needs treatment for TB or CM, the preferred ART regimen is the study-provided regimen of TDF/FTC/EFV. PIs are not recommended during TB treatment with rifampicin because of their interactions with rifampicin. If therapy with a PI is required during TB treatment, rifabutin should be used instead of rifampicin. Because of the potential for rifampicin to increase metabolism of ET and vincristine, it is recommended that rifabutin, if available, be substituted for rifampicin if participants are receiving either ET or vincristine.

7.18 Allergic Reaction/Hypersensitivity (PTX)

Any participants who experience severe or life-threatening symptoms of hypersensitivity will discontinue PTX permanently. For moderate symptoms, the PTX infusion should be stopped. Intravenous diphenhydramine 20 to 50 mg and intravenous dexamethasone 10 mg, or other appropriate therapy as per institutional guidelines, should be administered. The PTX infusion may be resumed after recovery of symptoms at a low rate (20 mL/hour for 15 minutes, then 40 mL/hour for 15 minutes, and then, if no further symptoms, at a full dose until the infusion is complete). If the symptoms recur the infusion must be stopped. For severe, life-threatening symptoms of hypersensitivity, the PTX infusion should be stopped. Intravenous diphenhydramine 20 to 50 mg and intravenous dexamethasone 10 mg, or other appropriate therapy as per institutional guidelines, should be administered. The addition of epinephrine or bronchodilators may be used if indicated.

7.19 Chemotherapy Extravasation

If there is evidence of chemotherapy leakage or swelling during or following intravenous administration of vincristine or PTX, local care should be provided as described in the A5263/AMC066 MOPS. For extravasation, surgical consultation could be considered.

7.20 Symptomatic Therapy for Toxicities

Symptomatic therapy including, but not limited to, analgesics, antihistamines, antiemetics, antidiarrheal agents, may be administered as deemed necessary by the investigator, unless specifically prohibited by the protocol.

7.21 Virologic Failure

Virologic failure is defined as two successive measurements of plasma HIV-1 RNA ≥ 1000 copies/mL at week 12 to week 24 or RNA ≥ 400 copies/mL at week 24 or later. Participants who have virologic failure during Step 1, 2, or 3 should have confirmatory samples drawn as soon as possible after the initial plasma HIV-1 RNA result but no later than the next scheduled study visit.

If a participant's viral load rises above 10,000 copies/mL, an ART change is required. The participant will be offered the best locally provided ART. Sites must contact the CMC to request permission to make any changes in ART.

7.22 Procedures in the Event of Contraceptive Failure, On-Study Pregnancy, or Breastfeeding

Contraceptive Failure

In the event of contraceptive failure, the use of an emergency contraceptive is an option. A levonorgestrel-only emergency contraceptive (i.e., Plan B) is preferred to minimize the occurrence of nausea, which may interfere with adherence to protocol medications. The use of EFV with an emergency contraceptive containing both ethinyl estradiol and levonorgestrel may cause significantly increased ethinyl estradiol levels (Stocrin package insert, 2006), thereby increasing the incidence of nausea and vomiting. Combined ethinyl estradiol/levonorgestrel emergency contraceptive is, however, an acceptable option if a levonorgestrel-only emergency contraceptive is unavailable.

On-Study Pregnancy

A5263/AMC066 will not provide perinatal care for women. Women who become pregnant will be referred to local clinics and/or other research studies for prenatal and postpartum care and sites are encouraged to add the participant to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Phone: +1-910-679-1598; Fax: +1-910-256-0637.

Monitoring for toxicity related to ART will continue during and after pregnancy. ART during pregnancy will follow the local standard of care.

Women who become pregnant **on study should follow local standard of care but may continue to receive study-provided ART.**

Women who are taking chemotherapy and become pregnant will immediately stop **study-provided** chemotherapy. Women who become pregnant and who continue to be followed in the study will be considered "on-study/off study-provided chemotherapy" during the time they are pregnant or breastfeeding. After pregnancy and/or breast-

feeding **are/is** completed, **consult the CMC to discuss resumption of study-provided chemotherapy.**

Pregnancy outcomes will be documented by completion of the appropriate CRF after the pregnancy has ended.

Breastfeeding

Breastfeeding is permitted in areas where formula feeding is not a viable option per WHO guidelines. Women who breastfeed will not receive chemotherapy. Breastfeeding participants receiving study-provided ART will be allowed to continue their use while breastfeeding at the discretion of the site investigator. Changes in ART for women who are breastfeeding will be at the discretion of the site investigator. EFV is used in HIV-exposed infants and HIV-infected children. Data on the use of TDF and other ART agents during breastfeeding are limited. Please refer to WHO guidelines in the A5263/AMC066 MOPS for women who breastfeed.

8.0 CRITERIA FOR DISCONTINUATION

8.1 Permanent Treatment Discontinuation

- Specified drug-related toxicity (see section 7.0).
- Requirement for prohibited concomitant medications (see section 5.5).
- Completion of treatment as defined in the protocol.
- Request by participant to terminate treatment.
- Clinical reasons believed life threatening by the site investigator, even if not addressed in the toxicity section of the protocol.

8.2 Temporary Treatment Discontinuation

- Chemotherapy will be discontinued during pregnancy and breastfeeding

8.3 Premature Study Discontinuation

- Request by the participant to withdraw.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant.
- Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self.
- At the discretion of the ACTG, IRB, Office for Human Research Protections (OHRP), NIAID, local government agencies, investigator, or pharmaceutical supporters.

9.0 STATISTICAL CONSIDERATIONS

At an interim review in March 2016, the CCDSMB found that the ET plus ART arm was less effective than the PTX plus ART arm. Per the CCDSMB recommendation, enrollment into this arm and all initiation of ET in subsequent steps were discontinued in March 2016.

The following statistical considerations apply only to the revised study as a two-arm trial, which includes the experimental arm (BV plus ART) and the active control arm (PTX plus ART). Refer to Version 2.0 of the protocol for the statistical considerations for the original three-arm trial.

9.1 General Design Issues

A5263/AMC066 is a prospective, randomized, active-controlled, **two-arm** clinical trial designed to estimate the difference in event (KS progression, death, entry into an additional step, or loss to follow-up, prior to week 48) rates between **an** “experimental” regimen (BV plus ART initiation, which **is** considered standard of care therapy in resource-limited settings) and an active control (PTX plus ART initiation, a standard treatment in the United States that is sometimes used as salvage therapy for relapsed/refractory KS in resource-limited settings) for the treatment of HIV-infected, ART-naïve participants presenting with advanced KS. After confirmation of eligibility, study participants are randomized in 1:1 fashion to one of the two arms. Randomization is stratified by CD4+ lymphocyte cell count (<100 versus ≥100 cells/mm³) and country.

The trial is designed to evaluate whether there is sufficient evidence to conclude BV plus ART is noninferior to PTX plus ART (i.e., the active control). Noninferiority is defined as demonstrating that the clinical 48-week PFS rate in the investigational arm is within 15% of the **PFS** rate of the PTX arm. The selection of the 15% noninferiority margin was a combination of clinical judgment and statistical reasoning. A poll of the sites was conducted to derive the “maximum treatment difference that is considered clinically irrelevant” (i.e., largest acceptable difference in order to gain the advantage (cost) of the experimental chemotherapy). However, the team realizes that this margin and thus the resulting interpretation of the estimates of between-arm differences is subjective and may be country/site-specific. The team further acknowledges that event rates could differ from assumed rates and that this could influence the interpretation of the results. For example, if the event rate in the active control turns out to be substantially smaller, then a 15 percentage point increase might be substantial (e.g., if the control rate is only **30%**, a 15 percentage point increase is a 50% relative increase). The team discussed the possibility of defining a “sliding” noninferiority margin as a function of the control group response rate but concluded that this was overly complex. The team realizes that the interpretation of trial results must be taken in context of many things including the observed control group response rate. The reporting of trial results will clearly incorporate and elaborate on these issues.

The experimental regimen has advantages relative to the active control. These include reduced costs and increased drug access. **The** BV regimen is **not** associated with cardiotoxicity, whereas PTX has been associated with arrhythmias. The BV combination is minimally myelotoxic, whereas PTX more frequently **is** associated with neutropenia. If the experimental regimen displays efficacy that is “not too much worse” than the active control, then **this** regimen may be suitable as a substitute for the active control, given the advantages of the experimental regimen.

Considerable deliberation was given to the endpoint selection issues in this trial. Selected endpoints should be clinically relevant (i.e., address the scientific question), easy to interpret, easy and affordable to obtain, measured in an unbiased manner, sensitive to changes induced by treatment, measured as objectively as possible, measured as consistently as possible to reduce variation (via standardization and centralized labs), and result in a reasonable sample size. Composite endpoints, combining component endpoints associated with KS and HIV-disease, were considered since this trial can be viewed as investigating treatment of participants with multiple diseases and interest lies in the totality of participant outcome (rather than the trial being viewed as an investigation of treatment for KS within HIV-infected participants). Thus composite endpoints can provide a more complete characterization of the treatment effect. They can also reduce bias due to competing risks and potentially improve power. KS progression, death, entry into an additional step, or loss to follow-up, prior to week 48 has been selected as the primary endpoint. Secondary composite endpoints have been constructed by sequentially adding the next most “severe” component of interest in KS-AIDS (AIDS-defining event, HIV-1 RNA virologic failure, KS-IRIS, and KS response).

Participants who originally have an **IERC-confirmed CR or PR** to Step 1 chemotherapy, but then progress at least 12 weeks after the last dose of Step 1 chemotherapy, will have the opportunity to enter Step 2 and be provided a second course of up to six cycles of the same chemotherapy utilized in Step 1 **if**, in the opinion of the investigator, **the participant** could potentially benefit from another course of the same chemotherapy.

Participants will have the opportunity to enter Step 3 (**assignment to the** chemotherapy arm not utilized in Step 1) when: (1) there is IERC-confirmed KS progression at any time during Step 1 chemotherapy; or (2) there is IERC-confirmed KS progression **fewer than** 12 weeks after the last chemotherapy dose in Step 1 in participants who have had an **IERC-confirmed CR or PR**; or (3) there is IERC-confirmed KS progression following Step 1 chemotherapy, without any prior response; or (4) there is IERC-confirmed KS progression in Step 2; or (5) **with concurrence of the CMC**, there is dose-limiting toxicity after receiving **fewer than** four cycles of chemotherapy in Step 1 or Step 2, in the absence of a CR or PR. Participants otherwise eligible for Step 2 who, in the opinion of the investigator **and with concurrence of the CMC**, are unlikely to benefit from another course of the same chemotherapy received in Step 1 will also be eligible for randomization in Step 3.

Participants who fail Step 3 will be offered **alternative care available locally, outside of the study**.

Participants who received ET while on study (see protocol version 2.0) will be followed for 144 weeks after beginning the last cycle of ET. All other participants will be followed for 96 weeks after randomization or assignment to the last step they enter.

9.2 Endpoints

9.2.1 Primary Endpoints

PFS defined as a lack of KS progression, death, entry into an additional step, or loss to follow-up, prior to week 48.

9.2.2 Secondary Endpoints

9.2.2.1 Death by week 48; KS progression by week 48

9.2.2.2 AIDS-defining event by week 48

9.2.2.3 HIV-1 RNA virologic failure by week 48

Virologic failure is defined as two successive measurements of plasma HIV-1 RNA ≥ 1000 copies/mL at week 12 to week 24 or RNA ≥ 400 copies/mL at week 24 or later.

9.2.2.4 KS-IRIS by week 48

9.2.2.5 KS tumor response

9.2.2.6 Duration of response

9.2.2.7 KS progression, death, or AIDS defining event by week 48

9.2.2.8 KS progression, death, AIDS defining event, or virologic failure by week 48

9.2.2.9 KS progression, death, AIDS defining event, virologic failure, or KS-IRIS by week 48

9.2.2.10 Time to KS progression or death

9.2.2.11 Time to death

9.2.2.12 Change in KS treatment by week 48

9.2.2.13 Chemotherapy-related toxicities and AEs (e.g., PN)

9.2.2.14 Changes in CD4+ lymphocyte cell count

9.2.2.15 Adherence to therapy

9.2.2.16 Plasma KSHV

9.2.2.17 PBMC KSHV

9.2.2.18 Presence of oral KS

9.2.2.19 RNA levels for KSHV genes

9.2.2.20 PN and SPN

9.2.2.21 Similar endpoints as above on other later steps

9.2.2.22 Immunohistochemical evaluations of viral and cellular gene expression

9.2.2.23 Quality of life measures

9.2.2.24 Cellular and humoral markers of immune function and activation

9.3 Randomization and Stratification

Step 1: After confirming eligibility, participants will be randomized in a 1:1 ratio to the **two** regimens. Randomization will be stratified by CD4+ lymphocyte cell count (<100 or ≥100 cells/mm³) and by country.

Step 2: There is no randomization in Step 2.

Step 3: Participants in Step 3 will be **assigned** to the remaining regimen **not utilized in Step 1**, using the same stratification factors as in Step 1.

Step 4: There is no randomization in Step 4.

9.4 Sample Size and Accrual

A5263/AMC066 is designed to evaluate if there is sufficient evidence to conclude BV plus ART is noninferior to PTX plus ART. Noninferiority is defined as demonstrating that the 48-week PFS rate in the investigational arm is within 15% of the PTX arm.

The primary **analysis** will consist of constructing a 95% confidence interval (CI) for the difference between event rates of **the** experimental arm (BV) with the active control (PTX) and noting whether the CI rules out more than a 15% increase in event rate of **the** experimental arm compared **with** PTX. **In the three-arm trial (protocol Version 2.0) two pairwise comparisons were planned, for which the** team considered acceptable

to control error rates at the contrast level (with two primary contrasts comparing each experimental regimen versus PTX) rather than controlling the trial-wise error rate. **Therefore, in the revised two-arm trial, the same approach will be used (i.e., controlling the error rate at the contrast level for the remaining treatment comparison).**

With **386** participants in the two-arm trial, the study has **80%** power to demonstrate noninferiority assuming the true event rates in both arms are 65% **(the sample size for the entire study, including those already randomized to ET in Step 1A under protocol version 2.0, is 446).**

This is based on the following assumptions:

- 15% noninferiority margin. The selection of the 15% noninferiority margin was a combination of clinical judgment and statistical reasoning. A poll of the sites was conducted to derive the “maximum treatment difference that is considered clinically irrelevant (i.e., largest acceptable difference in order to gain the advantages (e.g., cost) of the experimental chemotherapy)”. However, the team realizes that this margin and thus the resulting interpretation of the estimates of between-arm differences is subjective and may be country/site-specific.
- Two interim analyses and one final analysis are planned: The two interim evaluations will occur after approximately 33.3% and 66.7% of the planned enrollment has completed week 48 (thus having primary endpoint results, i.e., at 33% and 67% information). A Lan-DeMets spending function was used corresponding to the O'Brien-Fleming boundary. During the interim analyses, evaluation of efficacy and futility can be conducted (i.e., either hypotheses, H_0 or H_1 can be rejected but is nonbinding in terms of trial alteration).
- One-sided significance level $\alpha=0.025$
- 1:1 assigned fraction
- Inflation rate of 10% for loss-to-follow-up **for a known reason**

The point estimate of primary endpoint rate at week 48 for PTX is 65-70% (though it is not significantly different from PLD with a 50% PFS rate) according to Cianfrocca et al [44]. Sensitivity analyses were conducted to evaluate the power as a function of assumed primary endpoint (PFS) rate when the noninferiority margin is 15%.

9.5 Monitoring

The study statisticians and data manager will prepare biannual administrative reports. Administrative reports will include baseline summaries (combined by treatment arms) including demographics and will address issues concerning the viability and appropriate execution of the protocol such as accrual and endpoint evaluability.

Quarterly toxicity reports listing individual participant toxicity information (combined by treatment arms) will be prepared by the statisticians and data manager and will be forwarded to the **DAIDS Clinical Representative** and **protocol co-chairs**.

The CCDSMB will monitor A5263/AMC066 annually or twice annually. The study statisticians will prepare reports for the CCDSMB. CCDSMB reports will include all of the information in the Administrative Reports and the Toxicity Reports by randomized treatment. CCDSMB reports will also contain summaries of endpoint data by randomized treatment.

Moving forward, formal between-arm comparisons will occur at each interim CCDSMB review; corresponding CIs, based on percentage information, will be constructed for the difference in proportions between the experimental therapy and the active control. Predicted interval plots (PIP) [62,63] will be constructed to aid the CCDSMB in decision-making. The PIPs provide the CCDSMB with a prediction of the trial results were the trial to continue as planned under varying assumptions regarding future data. Event rates will be evaluated to determine whether sample size adjustments are warranted. The sample size will not be adjusted based on the effect size (e.g., between-group difference) but will be adjusted based only on the pooled response rate. If the rate is very different than anticipated, then the sample size could be adjusted at the discretion of the CCDSMB. Since sample size recalculation is based on a pooled response rate there is no concern for an inflation of Type I error. Possible recommendations of the CCDSMB include continuation of the trial as planned, the discontinuation of a specific arm(s) due to inferiority or safety concerns, discontinuation of the study, or a sample size adjustment.

“Noninferiority has not been demonstrated” does not necessarily imply inferiority, and in some cases more data may still be able to demonstrate noninferiority. Similarly “not superior or inferior” does not imply similarity or noninferiority.

For interim data monitoring, it is important that both the ITT and Per Protocol analyses qualitatively agree with respect to conclusions particularly if noninferiority claims are likely to be made. If the ITT and per protocol analyses are qualitatively different, then consideration of trial continuation is warranted so that more definitive conclusions can be reached. Consideration of the composite nature of the endpoint is also important (e.g., evaluation of the components of the composite is important) since one arm could have a lower event rate but the events could be more severe (e.g., deaths).

9.6 Statistical Analyses

The primary analyses will consist of the construction of a CI for the difference (**adjusted using the Lan-DeMets approach to account for the multiple interim analyses to provide 95% simultaneous coverage over the multiple analyses**) in the proportion of 48-week event rates between the experimental regimen and the active control (ART initiation with PTX). These analyses will utilize all randomized participants as per ITT principles and will be model adjusted for the stratification factors (country and CD4+ lymphocyte cell count). Missing data will be treated as failures since: (1) recent data reported at the ACTG meeting (2008) suggest that most missing data from international sites are due to participant deaths, and (2) the study participants have advanced stage

disease. Per-protocol analyses will be conducted as co-primary analyses given the noninferiority nature of the trial design.

The difference in 48-week event rates for secondary endpoints will be similarly constructed to compare **the** experimental regimen with the active control but without adjustment for the interim analyses. Regression analyses will examine treatment-by-stratum interactions to investigate if global estimates or stratum-specific estimates are appropriate. Analyses of the time-to-event endpoints will be conducted using proportional hazards regression controlling for the stratification factors in the model. A quality-of-life adjusted survival analysis will also be conducted using Q-TWIST methodology.

Additional analyses will be described in a statistical analysis plan that will be reviewed by the protocol team prior to any analyses of the trial data.

10.0 PHARMACOLOGY PLAN

Please refer to stand alone sub-study A5278s, "Pharmacology Substudies of A5263 and A5264", for the pharmacology plan. Sites are strongly encouraged to coenroll participants in A5278s.

11.0 DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

11.1 Records to Be Kept

Case report forms (CRF) **are** provided for each participant. Participants must not be identified by name on any CRFs. Participants **are** identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG Data Management Center upon randomization.

11.2 Role of Data Management

11.2.1 Instructions concerning the recording of study data on CRFs **are** provided by the ACTG Data Management Center. Each CRS is responsible for keying the data in a timely fashion.

11.2.2 It is the responsibility of the ACTG Data Management Center to assure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

11.3 Clinical Site Monitoring and Record Availability

Site monitors under contract to the National Institute of Allergy and Infectious Diseases (NIAID) will visit participating clinical research sites to review the individual participant records, including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.

The site investigator will make study documents (e.g., consent forms, drug distribution forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the NIAID, the OHRP, local government agencies, and the pharmaceutical supporters or designee for confirmation of the study data.

11.4 Expedited Adverse Event Reporting

11.4.1 Adverse Event Reporting to DAIDS

Requirements, definitions, and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website: <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual>.

The DAIDS Adverse Events Reporting System (DAERS) internet-based reporting system must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact **NIAID CRMS Support** at CRMSSupport@niaid.nih.gov or from within the DAERS application itself.

Sites where DAERS has not been implemented will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual>.

For questions about EAE reporting, please contact the RSC (RSCSafetyOffice@tech-res.com).

11.4.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, **is** used for this study.
- The study products for which expedited reporting **is** required are ET, bleomycin sulfate, vincristine sulfate, PTX, and any study-provided ART.
- In addition to the EAE Reporting Category identified above, other AEs that must be reported in an expedited manner are all grade 4 laboratory results

and any malignancy or myelodysplastic syndrome, serious IRIS events, and fetal losses. “Fetal loss” is defined on the PSWP.

- Overdoses of Atripla and EFV do not require expedited reporting, but will be reported to Merck every 3 months by the SDAC/DMC. Overdoses of Atripla and EFV should be recorded on the CRF and keyed in the database in a timely manner. “Overdose” is defined on the PSWP.

11.4.3 Grading Severity of Events

The DAIDS AE Grading Table, Version 1.0, December 2004 (Clarification, August 2009), must be used and is available on the DAIDS RSC website: <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables>.

11.4.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is from enrollment of a trial participant to the end of trial follow-up for that participant.
- After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions SUSARs, as defined in Version 2.0 of the EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

12.0 PARTICIPANTS

12.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix VI) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the participant (or legal guardian or person with power of attorney for participants who cannot consent for themselves). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant or legal guardian, and this fact will be documented in the participant's record.

12.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the

participant, except as necessary for monitoring by IRB, the NIAID, the OHRP, local government agencies, or the pharmaceutical supporters or designee.

12.3 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB, the NIAID, the pharmaceutical supporters, the OHRP, or other government agencies as part of their duties to ensure that research participants are protected.

13.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial **is** governed by ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical supporters prior to submission.

14.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association Dangerous Goods Regulations.

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APPENDIX I: ACCEPTABLE CONTRACEPTION METHODS AND DOCUMENTATION OF STERILIZATION, MENOPAUSE, AND CHILD'S OR ADOLESCENT'S REPRODUCTIVE POTENTIAL

1. Acceptable Contraception Methods; Please also refer to the FDA Birth Control Guide found at:
<http://www.fda.gov/ForConsumers/ByAudience/ForWomen/WomensHealthTopics/ucm117971.htm>

Category X Medications	Category D Medications ¹	Category C Medications
Contraception requirements as directed by drug package insert, medical alert, or investigator's brochure.	A Combination of TWO of the following methods: <ul style="list-style-type: none"> • Condoms (male or female) with or without a spermicidal agent. • Diaphragm or cervical cap with spermicide • IUD • Tubal ligation² • Hormone-based contraceptive 	At least one of the following methods MUST be used appropriately: <ul style="list-style-type: none"> • Condoms (male or female) with or without a spermicidal agent • Diaphragm or cervical cap with spermicide • IUD Hormone-based contraceptive

¹Exceptions for Some Drugs: Additional or specific requirements may be found in the package insert, medical alert, or investigator's brochure, e.g., the labeling for EFV, a class D drug, specifies that only the female study **participant** must use two contraception methods, one of which must be a barrier method. In such cases, all the relevant instructions must be included in the protocol.

NOTE: Some protocol-specified medications (e.g., PIs, NNRTIs) alter the metabolism of hormonal-based methods. This interaction may make hormone-based methods less effective. Therefore, alternative or an additional contraceptive method may be required.

²Tubal Ligation is considered a form of sterilization for class C drugs. For classes D and X if not otherwise specified in the package insert or IB, it is considered a form of contraceptive.

2. Acceptable Documentation of Hysterectomy and Bilateral Oophorectomy, Tubal Ligation, Tubal Micro-inserts, Vasectomy, and Menopause

For participants receiving protocol-specified Category C medications

- Participant-reported history

For participants receiving protocol-specified Category X and D medications

- Confirmation of the lack of reproductive potential is REQUIRED
- Written documentation or verbal communication from a clinician or clinician's staff documented in source documents of one of the following:

APPENDIX I (Cont'd)

- Physician report/letter
- Operative report or other source documentation in the participant record (a laboratory report of azoospermia is required to document successful vasectomy)
- Discharge summary
- Laboratory report of azoospermia for males only
- FSH measurement elevated into the menopausal range as established by the reporting laboratory.

NOTE 1: The female study **participant** cannot provide written proof of a male partner's vasectomy status since he is not usually enrolled in the same study to provide consent for release of this information. This criterion, the "laboratory report of azoospermia" should be removed from the list of acceptable documentation that female study **participants** can provide.

NOTE 2, for EFV only: If the female study **participant** reports a history of infertility based on one of the above categories but written documentation is not obtainable, or she states that her partner has had a vasectomy, the female study **participant** must agree to use at least one barrier method of contraception with a possible second method required at the discretion of the site study physician. Documentation of the study **participant**'s statement should be entered into the source document.

APPENDIX II: ASSESSMENT OF CIRCULATING LEVELS OF PRO-INFLAMMATORY AND ANGIOGENESIS-ASSOCIATED MOLECULES

1.0 OBJECTIVES

- 1.1 To compare the effects of randomized treatment on serum levels of inflammatory cytokines and/or molecules associated with angiogenesis.
- 1.2 To determine whether serum levels of cytokines and angiogenesis-associated molecules are associated with clinical response, immunological response (assessed by measuring CD4+ lymphocyte cell count), virological responses (assessed by measurement of HIV-1 and HHV8 viral load), and the development of IRIS.

2.0 BACKGROUND

The risk of developing several cancers, including Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), and cervical cancer is greatly increased in HIV infection. Effective ART has resulted in a decrease in most AIDS-associated cancers, as well as in other AIDS-defining conditions; HAART has been seen to result in a pronounced decrease in the incidence of KS, as well as those forms of NHL that are associated with Epstein-Barr virus (EBV) infection, such as primary central nervous system (CNS) lymphoma (1-6).

Angiogenesis related to tumor growth, in concert with other tumor supporting factors, has been associated with the development and progression of many cancers, including KS. Angiogenic factors can be released into the systemic circulation as a result of cancer and numerous studies have demonstrated that several angiogenesis regulator substances circulate in the blood and may function as tumor growth factors in cancer patients (7). Vascular endothelial growth factor (VEGF) levels appear to be increased in HIV-infected patients (8-10). Several studies have assessed VEGF levels in AIDS-associated KS (7, 9-11), with conflicting results, although published studies have typically involved small numbers of participants. Additionally, constitutive over-expression of matrix metalloproteinases (MMP) MMP-2 and MMP-9 has been seen in AIDS-KS (12), with treatment of AIDS-KS using the matrix MMP inhibitor COL-3 resulting in decreased serum levels of MMP-2 and MMP-9 (13). MMPs are a family of zinc-dependent endopeptidases that facilitate tumor invasion and metastasis by mediating the destruction of extracellular matrix proteins (14-17). MMP-2 (gelatinase A) and MMP-9 (gelatinase B) degrade collagen IV, the major component of basement membranes. In addition to VEGF and MMPs, several other factors have been shown to have angiogenesis-promoting properties, or to be associated with angiogenesis. These include chemokines (IL8 [CXCL8], MCP1 [CCL2]), cytokines (IL6, leptin), and other growth and angiogenesis-promoting factors (bFGF, PDGF, EGF, MMPs).

APPENDIX II (Cont'd)

3.0 RATIONALE

The recent availability of multiplexed immunometric assays has made possible the simultaneous assessment of several of these angiogenic factors, using small volumes (<500 µl) of serum/plasma. Interestingly, some agents used in HAART, especially PIs, have been seen to have anti-angiogenic and anti-inflammatory effects, which have the potential to inhibit tumor development and/or growth. These effects are independent of the ART properties of these drugs (18, 19). Therefore, ART drug use may result in decreased expression of circulating angiogenic factors and inflammatory cytokines. Additionally, infection with EBV and KSHV may contribute to angiogenesis and invasiveness directly or through paracrine mechanisms. EBV Latent Membrane Protein 1 (LMP-1) induces expression of MMP-9, COX-2, VEGF, FGF-2, and HIF-1 alpha (20, 21). HHV8 induces such molecules as well. Early events in viral infection, as well as expression of specific viral genes (K1) induce expression of MMP-9 and VEGF (22-24).

Pro-inflammatory cytokines also have been seen to be associated with the pathogenesis of AIDS-KS (25-27). For example, IL6 has been reported to contribute to the growth of AIDS-KS cells (25), and elevated levels of this and other inflammatory cytokines are seen in HIV infection (27). Therefore, HIV-driven inflammatory cytokine production has the potential to contribute to the growth of KS, and enhanced production of these and other KS-stimulatory molecules is believed to contribute to the development of KS-IRIS (28). However, there is little information available on levels of angiogenesis-associated or inflammatory cytokines in AIDS-KS IRIS. In fact, little is known about circulating levels of key inflammatory cytokines, such as IL17, in KS. Additionally, the effect of HAART on these inflammatory cytokines has not been clearly defined.

4.0 EVALUATIONS

Serum levels of cytokines and inflammation- and angiogenesis-associated molecules will be determined at the following study visits: pre-treatment (entry), and at 3, 24, and 48 weeks post treatment initiation. Initially, this will be done retrospectively for specimens from 20 participants that: 1) respond to treatment, 2) develop IRIS, or 3) progress without IRIS. If this initial analysis suggests a relationship between cytokines, inflammatory markers and/or angiogenesis molecules and KS response status, additional samples from a larger number of participants will be tested to confirm and extend the initial results. Subsequent studies could include the assessment of markers of microbial translocation, in addition to inflammation- and angiogenesis-associated molecules.

5.0 ANALYSES

The working hypotheses that will be tested are that: 1) the development of IRIS will be preceded/accompanied by increased levels of angiogenesis/inflammation-associated serum molecules, when compared to clinically defined non-responders or responders without IRIS, and 2) those who respond to treatment and do not develop IRIS will show relatively lower levels of angiogenesis/inflammation-associated molecules than either those who developed IRIS or did not show a clinical response to treatment.

APPENDIX II (Cont'd)

Levels of angiogenesis-associated molecules (VEGF, bFGF, IL6, IL8, MCP1, MMP-2, MMP-9), as well as of inflammatory (IL1 β), Th1 (IFN γ), Th17 (IL17, IL6, TNF α) and TH2 (IL10, IL4) cytokines will be assessed, using two custom multiplexed (Luminex platform) panels in this study (Table 1). The use of these assays (R&D Systems) will allow the simultaneous determination of serum levels of thirteen molecules associated with angiogenesis/inflammation by multiplex immunometric assay, minimizing sample volume and maximizing the information generated, both financially and in terms of serum volume utilized. This work will be done in the Martinez-Maza lab at UCLA, using a BioPlex 200 Luminex system. In addition to this, we will also quantify serum levels of neopterin (IBL International) and CRP (high sensitivity, Hemagen), two inflammation-associated biomarkers, by ELISA. Serum neopterin has been seen to be a good prognostic marker in AIDS-KS (29). A minimum of 500 μ l of serum is required for assessment of these inflammation- and angiogenesis-associated molecules and cytokines, using these assays.

Table 1. Cytokine and angiogenesis multiplex assay analytes, assay range and sensitivity (from R&D Systems)

Analyte	%CV*	Sensitivity **	xMAP Region	Panel (Base Kit)
VEGF	8.6	3.7 pg/mL	52	A
bFGF	6	6.3 pg/mL	54	A
IL6	0.2	4.9 pg/mL	32	A
IL8 (CXCL8)	3.2	3.6 pg/mL	36	A
MCP1 (CCL2)	8.3	2.9 pg/mL	78	A
TNF α	-	0.6 pg/mL***	77	A
IL17	6.1	3.4 pg/mL	20	A
IFN γ	5.2	4.5 pg/mL	75	A
IL4	-	1.8 pg/mL***	21	A
IL1b	5.5	2.7 pg/mL	6	A
IL10	6.5	3.0 pg/mL	50	A
MMP-2	-	25 pg/mL***	13	MMP
MMP-9	-	7 pg/mL***	47	MMP

* intra-assay variability (% CV), middle of detection range, for a typical assay (plate 5, SMART/INSIGHT study) carried out in the Martinez-Maza lab

** lowest routinely detectable standard, from work in the Martinez-Maza lab

*** lower limit of detection, as indicated by manufacturer

APPENDIX II (Cont'd)

LABORATORY CONTACT INFORMATION FOR THE ABOVE TESTING

Martinez–Maza Laboratory
UCLA AIDS Institute
BSRB Room 173
615 Charles Young Dr. South
Los Angeles, CA 90095-7563
Attn: Otto Martinez-Maza and Larry Magpantay
Phone: 310-206-6846
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APPENDIX III: IMMUNE RESPONSE TO HHV8 IN AIDS-ASSOCIATED KS**1.0 OBJECTIVES****1.1 Primary**

- 1.1.1 To determine anti-HHV8 specific T cell immune response in participants with AIDS-associated KS before and after ART.
- 1.1.2 To follow the trajectory of the anti-HHV8 T cell response at various time points after ART is started.
- 1.1.3 To correlate changes in the anti-HHV8 T cell response with both HIV and HHV-8 viremia at specific time points.
- 1.1.4 To correlate the magnitude of the anti-HHV-8 T cell immune response with clinical outcome.

1.2 Secondary

- 1.2.1 To explore changes in regulatory T cell frequency in participants developing KS-IRIS.
- 1.2.2 To evaluate CD8 T cell exhaustion before and after antiretroviral treatment and during the development of KS-IRIS.

2.0 BACKGROUND

KS is the most common malignancy in persons with AIDS. HIV co-infection is a strong predictor of development of KS in HHV-8 infected patients with a 10-year probability of 49.6% (1). It is posited that control of HHV-8 infection is largely mediated by T cell responses (2-4). Indeed, HHV-8-specific CD8 cells are rare in patients who progress to KS whereas this anti-HHV-8 immune response is frequent and diverse in patients who control the infection (5). HAART is recommended for all patients with AIDS-associated KS and has significantly lowered the rate of KS (6). Of interest is that KSHV-associated immune responses after HAART show a trend for increased CD8+ T cell production of IFN γ by ELISPOT (7). Recent studies, however, indicate that polyfunctional responses to HIV and other chronic virus infections including CMV and EBV are more indicative of host control of these viral infections (8). We have shown that HHV8 seropositive, HIV seronegative, normal donors have polyfunctional CD8+ T cell reactivity to immunodominant HHV8 peptides (9). Moreover, we have also found that CD4 regulatory T cells (Treg) can suppress anti-HIV polyfunctional T cell responses in HIV-infected persons (10). Thus, it is possible that HHV-8 specific immunity, particularly CD8+ T cell polyfunctional responses to HHV8, in HIV/HHV8 co-infected patients before and after antiretroviral treatment could correlate with HHV-8 viremia and clinical outcome. These

APPENDIX III (Cont'd)

responses could be at least partly under control of Treg (11, 12). Similarly, these HHV8-specific immunologic parameters could be central to the pathology of KS-IRIS. ACTG trials A5263/AMC066 and A5264/AMC067 will both enroll study HIV-infected participants not receiving ART, who are diagnosed with KS. A5263/AMC066 will investigate three different chemotherapeutic regimens plus ART for participants with advanced KS, while A5264/AMC067 will study ART alone or with delayed chemotherapy versus ART with immediate chemotherapy. The populations that will be studied in these two trials will be ideal for assessing HHV-8 specific T cell immune responses and how control of HIV viremia through ART can affect this response. Moreover, as some of these participants may develop KS-IRIS, we will be able to investigate HHV8-specific immune markers that could be important in IRIS pathogenesis.

3.0 RATIONALE

Since KS is a major form of AIDS and is postulated to be under the control of T cell immunity, it is important to fully understand the immunologic response to HHV8 in HIV-infected participants. This knowledge is important in understanding the pathogenesis and oncogenesis of HHV8, and in developing immune-based therapies for HHV8 infection and KS. Moreover, as KS-IRIS can present with significant morbidity in these participants, defining a role for HHV8-specific immunity behind this phenomenon is important not only in developing potential therapies, but in identifying immune markers that can predict increased risk in the development of IRIS.

4.0 EVALUATIONS

Anticoagulated blood for obtaining PBMC will be collected from a maximum of 50 participants at entry, and weeks 3, 12, 24, and 48 after ART initiation, and at KS-IRIS diagnosis for polyfunctional intracellular staining (ICS) and determining regulatory T cell frequency and CD8+ T cell exhaustion using flow cytometry. Blood will be processed for isolation of PBMC and cryopreserved at the clinical sites for later shipping to the University of Pittsburgh Immunology Specialty Laboratory (Pitt ISL).

5.0 ANALYSES

The working hypotheses that will be tested are that: 1) HHV-8 specific CD8+ T cell immune response, as measured by a polyfunctional ICS assay, will initially increase after starting ART leading to a decrease in HHV-8 viremia, but will decrease once HHV8 viremia is suppressed, and 2) KS-IRIS is associated with a decrease in the frequency of regulatory T cells and increased down-regulation in markers of CD8+ T cell exhaustion.

PBMC will be cocultured in the Pitt ISL with HHV-8 peptides and/or vaccinia or lentivirus vectors expressing HHV8 proteins in antigen presenting cells using autologous B cells (CD40L-IL4 stimulated) (9, 11-13). The HHV8 proteins are 15mers overlapping by 11aa for gB, LANA, K8.1 and K12; the vaccinia and lentivirus vectors express each of these, plus additional, KSHV proteins. Controls are mock-treated or vaccinia virus or lentivirus empty vector-infected B cells. CD107a, MIP-1 β , IL2, IFN γ , and TNF α immune mediators will be evaluated using intracellular staining (ICS) and flow cytometry (5). Plasma HHV-8

APPENDIX III (Cont'd)

DNAemia (real time PCR) will be assessed at similar time points and will be correlated with the magnitude of the immune response. HHV-8 specific CD8 T cell exhaustion will also be evaluated by expression of inhibitory receptors PD-1, LAG-3, and 2B4 at baseline, at a specific time point after antiretroviral treatment is started, and when a study participant is diagnosed as having KS-IRIS. Regulatory T cell frequencies (CD4+CD25hiFoxP3+ cells) will be obtained only at baseline and when KS-IRIS is diagnosed. The subset of participants for these immunologic assays will be determined after the KS outcome results are available in order to better correlate the immune responses with the varying KS outcomes.

Table 1

Variability of CD8+ and CD4+ T cell intracellular cytokine secretion of TNF α , IL-2, IFN γ , MIP1 β , and CD107 α after stimulation with different HIV antigens, with and without the presence of dendritic cells or with positive control (Staphylococcal Enterotoxin B and CEF – CMV/EBV/Influenza)

Immune Mediator		TNF α				IL2			
		Mean	Median	SD	Variance	Mean	Median	SD	Variance
CD8	<i>Control</i>	16.93	10.32	17.38	301.99	6.10	3.00	7.20	51.82
	<i>HIV Ag*</i>	3.44	0.42	14.98	224.26	3.14	0.25	14.30	204.38
CD4	<i>Control</i>	19.14	13.25	19.27	371.50	8.46	3.03	9.84	96.79
	<i>HIV Ag*</i>	5.01	1.57	13.35	178.28	3.29	0.26	15.29	233.86

Immune Mediator		MIP1 β				CD107 α			
		Mean	Median	SD	Variance	Mean	Median	SD	Variance
CD8	<i>Control</i>	4.89	1.04	5.91	34.91	17.85	10.36	18.84	354.76
	<i>HIV Ag*</i>	0.12	0.09	0.09	0.01	0.820	0.840	0.320	0.103
CD4	<i>Control</i>	0.68	0.16	0.81	0.66	3.93	1.510	4.703	22.12
	<i>HIV Ag*</i>	0.05	0.04	0.08	0.01	0.316	0.300	0.112	0.013

Immune Mediator		IFN γ			
		Mean	Median	SD	Variance
CD8	<i>Control</i>	14.40	9.09	14.42	207.97
	<i>HIV Ag*</i>	2.98	0.26	13.65	186.19
CD4	<i>Control</i>	6.15	3.63	6.56	43.01
	<i>HIV Ag*</i>	1.84	0.35	8.80	77.44

Values are % of CD8+ or CD4+ T cells secreting the immune mediator

APPENDIX III (Cont'd)

*Values under HIV Antigen include T-cell immune mediator secretion under different conditions (e.g., with and without the presence of dendritic cells)

LABORATORY CONTACT INFORMATION FOR THE ABOVE TESTING

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APPENDIX III (Cont'd)

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APPENDIX IV: ASSESSMENT OF TISSUE MICROARRAYS TO CHARACTERIZE PATTERNS OF VIRAL AND CELLULAR PROTEIN EXPRESSION IN RELATION TO OUTCOMES

1.0 OBJECTIVE

To determine the effects of randomized treatment on KS as a function of patterns of KSHV viral protein expression.

2.0 BACKGROUND

Patterns of KSHV viral proteins expression vary among KS tumors. The role of particular viral proteins in determining tumor behavior remains poorly understood. Some may contribute to proliferation, some may protect from activation of apoptotic pathways, and some may play a role in angiogenesis and invasiveness. Some KSHV viral proteins are coordinately regulated and thus some tumors show high levels of viral lytic protein expression and others show only viral latent gene expression.

3.0 RATIONALE

It seems possible that **participants** who respond to antiviral therapy alone may have a very different protein expression profile than **participants** who respond to cytotoxic chemotherapy. Tissue micro arrays make it possible to assess viral protein expression across diagnostic tumor specimens.

4.0 EVALUATIONS

Viral protein expression will be assessed on tissue microarrays prepared from initial diagnostic specimens. This will be done for 4 viral genes (LANA, vIL6, ORF8.1, ORF59). The array will be evaluated by pathologist and level of expression graded semiquantitatively (3+, 2+, 1+, no expression). These antigens have been selected because reagents which work are available and have been evaluated in prior studies. The tissue microarray will make it possible to evaluate other markers of interest as they arise.

5.0 ANALYSES

The working hypothesis that will be tested is that tumor response to therapies will be predicted by the presence of lytic viral protein expression markers (vIL6, ORF8.1, ORF59). Levels of lytic viral expression markers will be assessed relative to latent viral expression (LANA). The results will be assessed separately for each treatment. Several outcomes might be envisioned that would have considerable importance. For example, if 30% of participants respond to PTX and 30% respond ET, but participants with strong lytic infection consistently (75%) respond to ET and rarely (10%) respond to PTX, then participants with lytic infection might be treated with ET so as to maximize resources (ET is cheaper) and maximize response rate (ET is better in this subset). Alternatively, if participants with strong lytic infection consistently fail to respond to ET and only respond

APPENDIX IV (Cont'd)

to PTX (which is likely to be less expensive than oral ET), the use of PTX would maximize both the response rate and maximize the use of resources in participants with lytic infection.

LABORATORY CONTACT INFORMATION FOR THE ABOVE TESTING

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APPENDIX V: KAPOSI'S SARCOMA GENE EXPRESSION PROFILING: DETECTION OF KSHV RNA LEVELS IN KAPOSI'S SARCOMA (KS) TISSUES

1.0 OBJECTIVE

To determine the effect of the treatment on KSHV viral RNA levels in tumors we will be utilizing a RT-QPCR for KSHV

2.0 DESCRIPTION OF THE ASSAY

Changes in transcription are a fundamental hallmark of cancer progression and invaluable tools for characterizing cancer. In the case of KS, KSHV/HHV-8 has been identified as the etiological agent and this assay is designed to identify KSHV genes that might change in response to therapy. We will use reverse-transcription (RT) coupled to amplification using PCR to measure the RNA levels of all KSHV/HHV-8 RNAs in the tumor. This assay is a research test only and should not be used to make clinical decisions. The purpose of including this assay as part of this trial is to determine its usefulness as a prognostic marker.

RT coupled to amplification using PCR is widely recognized as the most sensitive method to detect the presence of specific RNAs. We will use RT-QPCR. This assay measures the amount of PCR product based on hybridization to a sequence-specific dual-labeled fluorogenic oligonucleotide (TaqMan) or intercalation of a fluorescent dye. Fluorescence is recorded at each cycle. So-called Ct-values indicate the cycle at which the fluorescence crosses a particular threshold (5 times standard deviation (SD) of the non-template control (NTC)). Hence, Ct-values indicate the abundance of a given RNA on a log scale. A low Ct value represents a highly abundant target RNA. We have experience doing these assays at the University of North Carolina and are currently performing similar assays for other AMC trials.

Specifically, total RNA will be isolated from each biopsy using RNeasy (Qiagen, Crawfordsville, Indiana) according to the supplier's protocol and reverse-transcribed using Mo-MuLV reverse transcriptase and 120 pmol random hexanucleotide primers (TaqMan, Applied Biosystems Inc., Foster City, CA). After incubation at 42°C for 35 min, the reaction will be stopped by heating to 95°C for 5 min, the cDNA pool diluted, and the resulting sample analyzed by RT-QPCR. We will use commercial SYBRgreen-based PCR (Roche Inc., Foster City, CA) as a uniform detection method.

3.0 SAMPLE SIZE

We have calculated the sample size based on expected differences in KSHV mRNA levels between responders and non-responders. This results in 138 participants (46 for each arm), which will be analyzed at baseline and 24-48 hours post-therapy. This yields 276 assays on trial.

APPENDIX V (Cont'd)

4.0 ENDPOINTS AND CONTRASTS

Baseline gene expression (\log_2 (mRNA levels)) will be compared between responders and non-responders for each of 96 genes. It is believed that there may be a gene*treatment interaction and thus it is envisioned that analyses will investigate the relationship between gene expression and response within treatment arm. Thus Type I error control for multiplicity is conducted within-arm.

Assumptions (within-arm)

1. Type I error = 5% (using Bonferroni adjustment for 96 tests)
2. Power = 90%
3. Equal number of responders and non-responders will be randomly selected

Minimally Relevant Between-Group Difference*	SD*	N/arm	Total N
5	3.5	46	138

* \log_2 scale

LABORATORY CONTACT INFORMATION FOR THE ABOVE TESTING

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APPENDIX VI
DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
SAMPLE INFORMED CONSENT
For protocol: A5263/AMC066

A Randomized Comparison of Three Regimens of Chemotherapy with Compatible Antiretroviral Therapy for Treatment of Advanced AIDS-KS in Resource-Limited Settings, A5263/AMC066, FINAL VERSION 3.0, dated 12/7/16

SHORT TITLE: Treatment of Advanced AIDS-KS in Resource-Limited Settings

INTRODUCTION

You are being asked to take part in this research study because you are infected with HIV, the virus that causes AIDS. It also appears that you have Kaposi's sarcoma (KS), a type of cancer associated with AIDS.

WHY IS THIS STUDY BEING DONE?

This study is being done to compare the safety and efficacy of **two** combination treatments for KS and AIDS. All of the drugs that **are** used in **this** study are approved by the US Food and Drug Administration (FDA) for the treatment of either KS or AIDS.

Approximately **446** participants will partake in this study.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

If you join this study and take etoposide (ET) while you are on the study, you will be in the study for about three years after you start the last cycle of ET. If you join this study and do NOT take ET while you are on the study, you will be in the study for about **two years after you start **your last step on the study**.** During this time, you will need to be seen in the clinic about 18 times in the first 12 months. After this time, the number and frequency of your visits will depend on how well your treatment is working for you. The required evaluations at each visit will take *(enter site's estimation of the study visit duration)* hours; the study staff will be able to **estimate** how long each visit will **take**. Details of the study procedures are in Attachment A (A5263/AMC066 STUDY VISITS).

If you decide not to take part in this study or if you do not meet the eligibility requirements, we will still use some of your information. As part of this screening visit, demographic (**for example**, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, HIV viral load) information is being collected from you so that ACTG researchers may determine whether there are patterns or common reasons why people do not join a study.

APPENDIX VI (Cont'd)

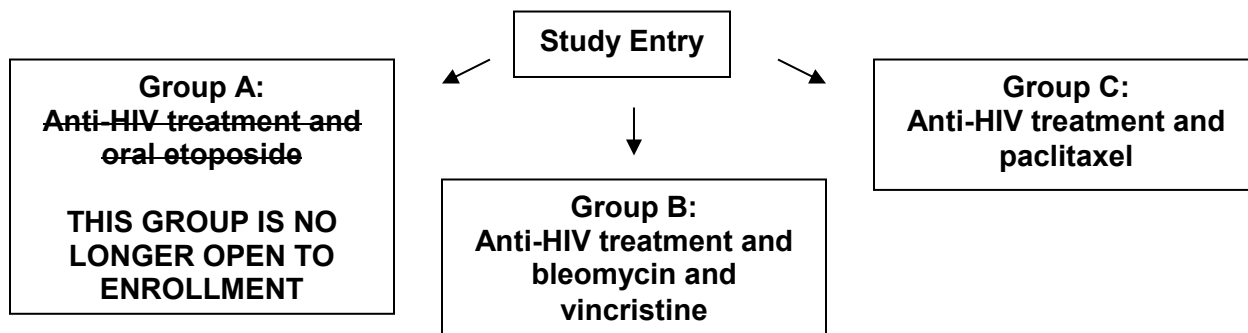
The information may also help ACTG researchers understand more about HIV and KS treatment.

When this study first started, the three KS treatments being studied were 1) paclitaxel (PTX), 2) bleomycin and vincristine given together (BV), and 3) etoposide (ET). These KS treatments are being studied in combination with anti-HIV medications. In March 2016, the DAIDS Co-Infections and Complications Data Safety Monitoring Board (CCDSMB) for A5263/AMC066 reviewed how participants were doing on the study. The CCDSMB is a group of people who are experts in the fields of medicine and statistics, none of whom are directly involved with the study. Their role is to review the conduct of the study and ensure the safety of participants. The CCDSMB found that participants receiving ET did not do as well as those receiving PTX. Therefore, participants starting the study are no longer offered ET as a study treatment.

If you are just starting this study, you may be assigned to either 1) PTX or 2) BV. If you have already started the study and are receiving ET, the investigator at the site will discuss with you whether or not you should change to a different KS treatment. He or she will also discuss this with investigators running the study. If you decide to change KS treatment, you will be able to stay on the study and receive another treatment that you have not had before (PTX or BV).

PTX plus antiretroviral therapy (ART) is a standard of care used in developed countries for treatment of KS and HIV infection. The standard of care at this site is *(Insert the standard of care for your site)*.

At the study entry visit, you will be assigned to one of the **two remaining** treatment groups:



Because your assignment is random, like the flip of a coin, you will have an equal chance of being in **each group**. You will not be able to choose your group, but you and your doctor, as well as the study staff, will know which group you are in.

APPENDIX VI (Cont'd)

Group A

Participants starting the study will no longer be offered ET as a study treatment. This information will apply to you only if you have already started the study and are receiving ET and you decide to continue this treatment:

If you are in group A, you will take one capsule containing 50 mg of ET twice a day for a week and then take no capsules for the next 2 weeks. A week of taking ET plus 2 weeks of not taking ET is a cycle. If you are not having any problems from the ET, the dose will be increased to 100 mg (2 capsules) in the morning and 50 mg (1 capsule in the evening) for 1 week during the second cycle, followed by 2 weeks with no ET. If you are not having any problems from ET after the second cycle, in the third cycle the ET dose will be increased to 100 mg (2 capsules) of ET twice a day for a week followed by 2 weeks of not taking ET. You will receive a total of six cycles of treatment.

Group B

If you are in group B, you will get BV by injection into a vein in your arm. An intravenous catheter **is** inserted into an arm vein before each treatment. Vincristine is given first by a short (1 minute) injection. Then bleomycin is given over about 10 minutes. BV **is** given once every 3 weeks for a total of 6 doses.

Group C

If you are in group C, you will get PTX by injection into a vein in your arm. An intravenous catheter **is** inserted into an arm vein before each treatment. PTX **is** given once every 3 weeks for a total of 6 doses. The treatment takes about one hour.

You and your doctor will decide which anti-HIV drugs you should take. The drugs provided by the study are:

- Efavirenz (EFV, Stocrin) once a day
- Emtricitabine (FTC, Emtriva) once a day
- Tenofovir (TDF, Viread) once a day

You may use different drugs from the ones above, but they will not be provided through this study. If you cannot tolerate EFV, the study recommends that you take nevirapine (NVP, or Viramune) instead, but NVP will not be provided through the study.

Anti-HIV and anti-cancer drugs after the study

After you complete your study visits to 96 weeks after Step 1 entry, the study will no longer provide you with anti-HIV or anti-cancer drugs. At that time, you may have to stop a drug combination that has worked well for you, either because you cannot afford the treatment or because those drugs are not available in your country. Efforts will be made by your doctor to find a way to continue anti-HIV and anti-cancer drugs after the study is over.

Other

If you agree, some of your blood and KS biopsy specimens that are left over after all required study testing is done may be stored (with usual protectors of your identity) and used for US National Institutes of Health (NIH)-approved HIV-related research.

APPENDIX VI (Cont'd)

Please initial one of the following boxes to indicate whether or not you wish to have your specimens stored for research in the future:

☐ Yes, I agree to have my specimens stored for future research

☐ No, I do not want to have my specimens stored for future research

You can decide to withdraw your permission for the storage and use of your samples for future research whenever you want and we will destroy your samples. If you decide to withdraw your permission, contact the research staff at your site. Researchers will not be able to destroy samples or information from research that is already underway.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- the study is stopped or canceled
- you are not able to attend the study visits as required by the study
- **your primary care doctor thinks that participating in this study is no longer in your best interest**

The study doctor may also need to take you off anti-HIV drugs or anti-cancer drugs without your permission if:

- continuing one or more of these drugs may be harmful to you
- you need a treatment that you may not take while taking these drugs
- you are not able to take these drugs as required

It is possible that your doctor may take you off study drugs, but not off the study if:

- you become pregnant
- you breastfeed

WHAT ARE THE RISKS OF THE STUDY?

Risk of Study Medications

Anti-HIV drugs and anti-cancer drugs may have side effects, some of which are listed in Attachment B (A5263/AMC066 – RISKS AND BENEFITS). Please note that these lists include only the more serious or common side effects with a known or possible relationship. If you have questions concerning additional drug side effects, please ask the medical staff at your site.

APPENDIX VI (Cont'd)

Risk of Blood Draw and Having an Intravenous Catheter

Taking blood, inserting an intravenous catheter, and having an intravenous catheter in your arm may cause some discomfort, bleeding, bruising or swelling where the needle enters the body. In rare cases it may cause fainting or infection.

Risk of Participating in This Study

It is possible that participating in this study will make it difficult for you to keep your HIV status secret from people close to you. This may lead to unwelcome discussions about or reactions to your HIV status. Please talk with the clinic staff if you have any concerns in this regard.

Risk of Non-Study Medications

There is a risk of serious and/or life-threatening side effects when certain medications are taken with anti-HIV drugs. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before you take any medications. You must also tell the study doctor or nurse before taking any non-study therapies while you are on the study. Deaths have occurred when HIV-infected people have taken therapies such as herbs with anti-HIV drugs. In addition, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Pregnancy

The drug or drug combinations in this study may be unsafe for unborn babies. The risks to unborn babies for each drug are listed in Attachment B. If you are having sex that could lead to pregnancy, you must agree not to become pregnant or make a woman pregnant.

When you are taking EFV and/or anti-cancer drugs, you must use two methods of birth control that you discuss with the study staff. One method must be a barrier method. You must continue to use both methods of birth control until 12 weeks after stopping EFV or the anti-cancer drug.

If you are a man, you must agree to use condoms. Your female partner must use at least one additional birth control method.

If you are a woman, **you may choose from any of the following birth control methods:**

- Birth control drugs that prevent pregnancy given by pills, shots, or placed on or under the skin
- Male or female condoms with or without a cream or gel that kills sperm
- Diaphragm or cervical cap with a cream or gel that kills sperm
- Intrauterine device (IUD)

If you are a woman and are unable to use two methods, your doctor will talk with you about your options.

If you do become pregnant, you will be taken off chemotherapy, but will remain on study. You may also need to change the type of HIV medicine you are taking.

APPENDIX VI (Cont'd)

If you are taking anti-HIV drugs when you become pregnant, your pregnancy may be reported to an international database that collects information about pregnancies in women taking anti-HIV drugs. This report will not use your name or other information that could be used to identify you.

WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV or KS.

Your health will be followed more closely than usual while you are on the study, which may help you to feel better. Laboratory tests to monitor the effects of the **study** drugs will be provided by the study.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

[Insert general information about HIV/AIDS and KS treatment availability in your country or locale.]

Anti-HIV and anti-cancer drugs, laboratory tests to monitor how well these drugs are working, and quality medical care may or may not be available to you outside the study. The clinic staff will discuss with you other treatment choices in your area and the risks and the benefits of all the choices.

WHAT ABOUT CONFIDENTIALITY?

The study team will provide you with an identification number. This identification number (not your name or other information that could be used to identify you) will be used for laboratory tests or blood work stored for testing in future studies. Your medical records and the list of names, addresses, and identification numbers will be kept in a locked room. Only the study staff will have access. Any publication of this study will not use your name or identify you personally.

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your records may also be reviewed by (insert name of site IRB), ethics committee, NIH, the Office for Human Research Protections (OHRP), your country's national health agency, study staff, study monitors, and the drug companies supporting this study.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

APPENDIX VI (Cont'd)

WHAT ARE THE COSTS TO ME?

There **is** no cost to you for study-related visits, physical examinations, laboratory tests or other procedures. You, your insurance company, or your health care system may need to assume the cost of anti-HIV drugs not provided by the study. *[delete references to insurance company or health care system if not applicable at site]*. In some cases, it is possible that your insurance company or health care system will not pay for these costs because you are participating in a research study. *[Insert site/country policy]*

WHAT HAPPENS IF I AM INJURED OR, IF I BECOME PREGNANT, MY BABY IS INJURED?

If you or your baby is injured as a result of your being in this study, you or your baby will be given immediate treatment for injuries, and be referred for further treatment, if necessary. However, you may/may not (*per site/country policy*) have to pay for this care. There is no program for compensation either through *[this institution]* or the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A VOLUNTEER IN A RESEARCH STUDY?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled. You will still be able to receive drugs to treat your HIV and your KS outside this study.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- *Name and telephone number for the investigator or other study staff*

For questions about your rights as a **participant** in a research study contact:

- *(Name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site*
- *Telephone number of above)*

APPENDIX VI (Cont'd)

SIGNATURE FOR A5263/AMC066 INFORMED CONSENT

If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to take part in this study, please sign your name below.

Participant's Name (print)

Participant's Signature and Date

Participant's Legally Authorized
Representative (print)
(As appropriate)

Participant's Legally Authorized
Representative's Signature and Date

Study Staff Conducting Consent

Study Staff Signature and Date Discussion (print)

Witness's Name (print)
(As appropriate)

Witness's Signature and Date

APPENDIX VI (Cont'd)

ATTACHMENT A: A5263/AMC066 STUDY VISITS

The study staff can answer any questions you have about individual study visits or about the evaluations that will occur. The table below can be used as a quick reference for you, along with the explanations that follow.

I. Study Schedule

Evaluation or Procedure	Screening ¹	Entry ²	24-48 Hours After Second Chemotherapy Cycle Begins	Most Other Visits ³	Special Visit ⁴	Discontinuation ⁵
Consent	✓					
Contact Info Collected	✓					
Clinical Assessment	✓	✓		✓	✓	✓
KS Exam	✓	✓		✓	✓	✓
Skin Biopsy	✓	✓	✓		✓	
Laboratory Tests	✓	✓	✓	✓	✓	✓
Urinalysis		✓				✓
Pregnancy Test	✓	✓	✓	✓	✓	✓
Chest X-Ray	✓				✓	
Blood Oxygen Level	✓			✓		
Photographs of Your Skin		✓				✓
Neuropathy Exam	✓	✓		✓		
Questionnaires		✓		✓	✓	✓

¹ Screening Visit: After you have read and signed the consent form, you will have several evaluations done to make sure that you meet the requirements for joining the study.

² Entry Visit: If you are eligible to join the study, you will come to the clinic to enter the study and receive your treatment assignment. At this visit you will find out what anti-cancer drug you will **take**.

³ Most Other Visits: Most people will return to the clinic every three weeks for the first 12 months and then **every** 12 weeks for the next 12 months. Most people will then return to the clinic **one more time** the next **year**.

⁴ If at any point during the study you are found to have Immune Reconstitution Inflammatory Syndrome (IRIS), you will have the evaluations listed on the table under the heading of "Special Visit". Your study staff can **provide** further information on IRIS.

⁵ Discontinuation: If, for any reason, you or your doctors decide you cannot complete all of the study visits, you will be asked to come in for an extra visit.

APPENDIX VI (Cont'd)

II. Explanation of Evaluations

Consent and Contact Information Collected

- After you read the consent and have had a chance to ask questions about the study, you will sign the consent form if you want to continue to be evaluated for study participation.
- You will also be asked how to be contacted in case you miss a visit or there are problems with your tests, and whether you give the study team permission to contact you.

Clinical Assessments

- At all visits you will be asked about your health and any medicine you have taken in the last 60 days.
- At the screening visit, you will have a complete physical exam that will include measurement of weight and height, examination of the skin, head, mouth, and neck, listening to the chest, heart exam, belly exam, and examination of your legs and feet for swelling. The complete physical exam will also include signs and symptoms of diseases, diagnoses, and vital signs (temperature, pulse, respiration rate, and blood pressure).
- At all follow-up visits you will have a brief physical exam as needed. The clinic staff will check your vital signs such as weight, temperature, blood pressure, breathing, and pulse.

KS Exam

The study doctor or nurse will thoroughly examine your skin, lymph nodes (bumps in your neck, underarms and groin), and mouth for KS lesions. He or she will measure some of the KS lesions, count them, and may take photographs of the lesions to document their appearance.

Skin Biopsy

A biopsy is the process of cutting out a small piece of skin. The area of the skin where the sample will be removed is numbed with a local anesthetic. These biopsies are done to look at the amount of KS herpesvirus (KSHV), the virus that causes KS in the skin. A total of up to 3 skin biopsies **are** required. If your KS gets worse during or after the first chemotherapy treatment or if your KS appears to have healed completely, site staff will ask you to have more skin biopsies.

Laboratory Tests

Blood will be collected from you for various tests during the study. These include: safety lab tests, HIV viral load (a test that shows how much HIV is in your blood), and CD4 count (a test that shows how many infection-fighting cells you have in your blood). In addition, some of the blood that is collected will be stored for future study-related testing, including measuring the amount of KSHV and certain proteins in your blood. Some of the future testing has not been determined yet. Between 15 and 65 mL (1 to 4.5 tablespoons) of blood may be collected at any one visit.

APPENDIX VI (Cont'd)

Urinalysis

You will be asked to give a urine sample so that the appearance, concentration, and content of your urine can be tested.

Pregnancy Test

- If you are a woman able to become pregnant, a urine or blood pregnancy test will be done at these visits to make sure that you are not pregnant and at any visit if pregnancy is suspected.
- You will be given the results of this test as soon as it becomes available.

Chest X-Ray

- A chest X-ray is a picture of the chest that shows your heart, lungs, airway, blood vessels, and lymph nodes. A chest X-ray also shows the bones of your spine and chest, including your breastbone, ribs, collarbone, and the upper part of your spine. A chest X-ray is the most common imaging test or X-ray used to find problems inside the chest.
- **A chest X-ray will be repeated if you enter a new step of the study or if your KS gets worse.**

Blood Oxygen Level (if you are receiving bleomycin during the study)

This is a simple measurement of the amount of oxygen in the blood. It involves putting a plastic device on a finger and takes less than a minute. The oxygen level **is** checked when you are at rest. You will then need to exercise for a short while (either walk around or walk up some stairs) to make your heart beat faster before doing the test again.

Photographs of Your Skin

Photographs **are** taken during the study to show how the KS is changing. If your KS gets better or gets worse, more photos will be taken. At no time will your entire face appear, and any distinguishing features will be removed from the photo so that you cannot be identified. Only your patient identification number will be used to identify the photo.

Neuropathy Exam

You will have two neuropathy exams. If you receive vincristine or PTX, you will have up to 5 additional neuropathy exams. Neuropathy is a condition that can cause pain, numbness, and/or pins and needles in your feet and/or hands. You will be asked about how your hands and feet feel. You will also have your reflexes checked and will be checked to see how well you feel vibrations

Questionnaires

- You will be asked about how well you have taken your HIV medicine over the past few days.
- **If you have already started the study and are receiving ET and you decide to continue this treatment**, you will be asked about how well you are taking that medicine.
- At some visits you will also be asked about how you are feeling and how your daily activities are going. This will take an additional 10 minutes.

III. Disease Progression

Step 2

If your KS gets better but then worsens within 12 weeks or longer after you have completed your cycles of chemotherapy, your doctor may choose to treat you a second time with the same chemotherapy. If this happens, you will need to have the evaluations listed under entry on the table above done again. You will then follow the same schedule as listed in the table above. You will then receive another six cycles of chemotherapy. **If you completed one course of ET in Step 1, you will not receive a second course of ET. Instead you will enter into Step 3.**

Step 3

If your doctor does not choose to treat you with the same chemotherapy or if your KS gets worse after you are treated with the first chemotherapy regimen a second time, you will be **given the other chemotherapy regimen**. If this happens, you will need to have the evaluations listed under entry done again. You will then follow the same schedule as listed in the table below. **If you received ET in Step 1 or Step 2, you will be randomly assigned (like flipping a coin) to receive BV or PTX.**

Step 4

If you received ET prior to the decision to stop using ET in this study, it is possible that **your** KS will get worse after receiving a second regimen of chemotherapy. If this happens, your doctor can choose to give you the third study-provided chemotherapy or start you on chemotherapy not provided by the study. **If you are taking ET now, you may want to switch to a different chemotherapy, even if your KS is not getting worse. You can make this decision along with your doctor, and you will be given the third study-provided chemotherapy.**

If you are started on chemotherapy not provided by the study, your schedule will remain the same as it was on the previous chemotherapy. If you start the third study-provided chemotherapy, you will need to have the evaluations listed under entry done again. You will then follow the same schedule as listed in the study schedule above to week 24. After week 24, you will only have to come to the clinic every 12 weeks for follow-up.

APPENDIX VI (Cont'd)

ATTACHMENT-B: A5263/AMC066 RISKS & BENEFITS

Risks from Anti-HIV Drugs

Anti-HIV Drug or Class	Possible Side Effects
Any	<p>Changes in body shape, such as:</p> <ul style="list-style-type: none"> • Increase in fat around the waist and stomach • Increase in fat on the back of the neck • Thinning of the face, legs, and arms • Breast enlargement <p>Immune Reconstitution Syndrome: In some people with advanced HIV infection, signs and symptoms of inflammation from other infections may occur soon after anti-HIV treatment is started.</p>
Efavirenz (EFV, Stocrin)	<p>A small number of people may experience the following serious psychiatric problems:</p> <ul style="list-style-type: none"> • Depression, which may be severe • Suicidal thoughts or attempts (rarely) • Aggressive behavior • Psychosis-like symptoms, such as abnormal thinking, paranoia, and delusions. People with a history of psychiatric problems may be at greater risk for these serious psychiatric problems. <p>Side effects associated with the central nervous system may include the following:</p> <ul style="list-style-type: none"> • Dizziness • Trouble sleeping • Abnormal dreams • Drowsiness • Confusion • Difficulty concentrating • Hallucinations • A feeling of strangeness and losing touch with reality • An exaggerated feeling of well-being • Agitation or anxiety <p>If alcohol or mind- or mood-altering drugs are used with EFV, it is possible that the central nervous system side effects could become worse.</p> <p>Serious liver problems and worsening liver disease can occur. These problems can be life-threatening. People with these conditions may have abnormal liver function tests. If you are developing liver problems, you may have one or more of the following: yellowing of the skin or whites of your eyes, dark urine, pain on the right side of your stomach, loss of appetite, upset stomach or vomiting, pale colored stools, itchy skin.</p>

APPENDIX VI (Cont'd)

Anti-HIV Drug or Class	Possible Side Effects
	<p>Additional side effects include:</p> <ul style="list-style-type: none"> • Rash, which in rare cases may be severe • Upset stomach • Loose or watery stools • Headache • Pancreatitis (inflammation of the pancreas), with one or more of the following: stomach pain, nausea or vomiting • Hepatitis (inflammation of the liver) • Abnormal increases in pancreatic and liver enzyme levels in the blood • Abnormal increases in the amount of triglycerides and cholesterol in the blood • Abnormal vision • Fever <p>A false-positive urine-screening test for marijuana has been seen with one particular test brand and has not been seen when using other screening tests or with tests used to confirm results for marijuana.</p> <p><u>Efavirenz and Pregnancy</u></p> <p>The use of this drug during pregnancy and especially early pregnancy should be avoided. Efavirenz may cause fetal harm when taken during the first three months of pregnancy. Serious birth defects, including those of the central nervous system, have been seen in the offspring of animals and women on efavirenz.</p>
Nucleoside and Nucleotide Analogues (Emtricitabine and Tenofovir Disoproxil Fumarate are nucleoside analogues or closely related drugs)	<p>Lactic acidosis and severe hepatomegaly (enlarged liver) with steatosis (fatty liver) that may result in liver failure, other complications, and death have been reported with the use of antiretroviral nucleoside and nucleotide analogues alone or in combination. The liver complications and death have been seen more often in women on these drug regimens. Some nonspecific symptoms that might indicate lactic acidosis include unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, cramps, muscle pain, weakness, dizziness, and shortness of breath.</p>
Emtricitabine/ Tenofovir Disoproxil Fumarate (FTC/TDF, Truvada)	<p>No new or unexpected side effects are observed with the FTC 200 mg/TDF 300 mg combination tablet than those observed when each drug is given separately (see below).</p> <ul style="list-style-type: none"> • Headache • Dizziness • Generalized weakness • Depression • Worsening or new kidney damage or failure • Shortness of breath • Tiredness • Inability to sleep, unusual dreams • Loose or watery stools

APPENDIX VI (Cont'd)

Anti-HIV Drug or Class	Possible Side Effects
	<ul style="list-style-type: none"> • Upset stomach (nausea) or vomiting • Abdominal pain • Rash, itching, which sometimes can be a sign of an allergic reaction • Skin darkening of the palms and/or soles of the feet • Increased cough • Runny nose • Allergic reaction: symptoms may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath, a general feeling of illness or a potentially serious swelling of the face, lips, and/or tongue • Abnormal liver function tests, which could mean liver damage. If you are developing liver problems, you may have one or more of the following symptoms: <ul style="list-style-type: none"> ◦ Yellowing of the skin or whites of your eyes ◦ Dark urine ◦ Pain on the right side of your stomach ◦ Loss of appetite, upset stomach or vomiting ◦ Pale colored stools ◦ Itchy skin • Increases in pancreatic enzyme (substances in the blood), which could mean a problem with the pancreas • Increased triglycerides • Bone pain and bone changes such as thinning and softening which may increase the risk of breakage • Muscle pain and muscle weakness • Increased creatine phosphokinase (CPK), which could mean muscle damage <p>NOTE: If you are infected with both Hepatitis B and HIV, you should be aware that your liver function tests may increase, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen if emtricitabine is stopped.</p> <p>NOTE: Because there is only a small amount of information on tenofovir in pregnant women, tenofovir should be used during pregnancy only if clearly needed.</p>

Risks from Anti-Cancer Drugs

Anti-Cancer Drug	Possible Side Effects
Any Anti-Cancer Drug	Chemotherapy drugs are harmful to the unborn and should not be used

Anti-Cancer Drug	Possible Side Effects
Etoposide (Etopophos, Vepesid)	<p>Participants starting the study will no longer be offered etoposide as a study treatment. This information will apply to you only if you have already started the study and are receiving etoposide and you decide to continue this treatment:</p> <ul style="list-style-type: none"> • Lowering of blood counts, such as lowered white blood count which may make you more susceptible to infection • Lowered red blood counts which may result in fatigue, weakness or light-headedness • Lowered platelet counts which may result in increased risk of bleeding. • Serious allergic reactions. Symptoms may include: trouble breathing, fever, nausea, vomiting, chills, shakes, skin rash, blood in your urine, swelling in your hands and feet. • Some cancer drugs, including ET, appear to cause a small number of people to later develop blood disorders including acute leukemia after treatment. • Hair loss, sometimes as much as complete baldness. This may lead to others knowing that you are sick. • Nausea and vomiting, abdominal pain, diarrhea, decreased appetite, and weight loss • Mouth sores • Potential harm to unborn children when it is given to a pregnant woman <p>Do not break or open an etoposide capsule. The medicine from a broken capsule can be dangerous if it gets in your eyes, mouth, or nose, or on your skin. If skin contact occurs, wash the area with soap and water or rinse your eyes thoroughly with plain water.</p> <p>Avoid eating grapefruit or drinking grapefruit juice while being treated with this medication unless your doctor instructs you otherwise.</p>
Bleomycin (Blenoxane) and Vincristine (Oncovin)	<ul style="list-style-type: none"> • If vincristine leaks from the vein, it can cause serious burning and ulcers in the skin. We will take care to prevent this from happening, but even with care sometimes the drugs leak into the skin. If this happens, we will treat you to try to prevent serious injury. • Scarring of the lung from bleomycin • Peripheral neuropathy (numbness, tingling, and pain usually in the fingers or toes) • Pain or discomfort at the site where the drug is given into the vein. • Mouth sores • Hair loss • Nausea and/or vomiting • Chills, body aches and shaking (usually from bleomycin) • Skin rashes and rarely scarring

APPENDIX VI (Cont'd)

Anti-Cancer Drug	Possible Side Effects
Paclitaxel	<p data-bbox="358 384 974 411">IMPORTANT WARNING ABOUT PACLITAXEL</p> <ul data-bbox="358 436 1507 499" style="list-style-type: none"> • Paclitaxel can cause serious side effects including death • Serious allergic reactions (anaphylaxis) can happen in people who receive paclitaxel <p data-bbox="358 554 1518 651">Anaphylaxis is a rare, but serious medical emergency that can lead to death and must be treated right away. Everyone will be given medicine to lessen your chance of anaphylaxis. This medication is effective for most people, but anaphylaxis can still happen.</p> <p data-bbox="358 720 1438 783">Tell your healthcare provider right away if you have any of these signs of an allergic reaction:</p> <ul data-bbox="358 808 1334 905" style="list-style-type: none"> • Trouble breathing • Sudden swelling of your face, lips, tongue, throat, or trouble swallowing • Hives (raised bumps) or rash <p data-bbox="358 959 753 987">Additional side effects include:</p> <ul data-bbox="358 1012 1555 1461" style="list-style-type: none"> • Lowering of your blood cell counts that could cause infection, easy bruising and bleeding, or anemia • Tiredness • Bruising or bleeding • Nausea and vomiting • Slow or irregular heartbeat or fainting • Hair loss • Numbness, burning, or tingling in the hands or feet • Mouth or lip sores (mucositis) • Stomach pain, which can be severe • Diarrhea, which can be severe • Irritation at the injection site • Low blood pressure (hypotension)

Other Risk InformationImmune Reconstitution Inflammatory Syndrome (IRIS)

While being treated with anti-HIV drugs, your immune system's strong response to an opportunistic infection (OI) (an infection that you get because the HIV has lowered the strength of your immune system), may cause illness. This is called immune reconstitution inflammatory syndrome (IRIS). Usually, it causes a return or worsening of at least some of the symptoms you may have had before starting anti-HIV drugs.

Some examples of what could happen are:

- your lymph nodes (small organs in your body that help filter disease germs from the blood) could swell up

APPENDIX VI (Cont'd)

- you could get a high fever
- if you are being treated for a lung infection, you might have worsened cough and shortness of breath

While some of these reactions can be serious, they usually last for a short time and can be treated without stopping the anti-HIV drugs. If any of these reactions happen to you, you will be treated for the problem and asked to have some additional blood drawn for testing of your immune system at that time.

Pregnancy & Breastfeeding

It is not known if some of the drug combinations in this study would harm unborn babies. Tests in pregnant animals do show some risks for some drugs. If you are having sex that could lead to pregnancy, you must agree not to become pregnant, or, if you are a man, you must agree not to attempt to make a woman pregnant or participate in sperm donation. Pregnancy tests will occur at study entry and prior to all chemotherapy.

If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices and refer you to a provider of prenatal care if you do not have one. If you decide to continue in A5263/AMC066, you will continue to have study evaluations as described above. However, you will no longer receive study chemotherapy. If you are taking efavirenz (a medicine for your HIV) and become pregnant, you must immediately stop efavirenz and take a different HIV medicine. Your study doctor will decide which HIV drug you should take instead efavirenz and whether you should start efavirenz again after the pregnancy. The A5263/AMC066 study will not provide or pay for care related to your pregnancy or the delivery of your baby.

Biopsy

The potential risks of having a punch biopsy are:

- discomfort and/or pain at the site
- bleeding at the site
- infection at the site (this is rare)
- a small scar at the site

Benefits

Information learned from this study may help others who have KS and are infected with HIV. Information learned from this study may also help improve the ability of people to get anti-HIV drugs, by identifying drug combinations that cost less but are as effective as more expensive drug combinations.