SUMMARY OF CHANGES

Randomized, Phase II Trial of CHOP vs. Oral Chemotherapy with Concomitant Antiretroviral Therapy in Patients with HIV-associated Lymphoma in Sub-Saharan Africa
Version 8.0

NCI Protocol #: AMC-068
Local Protocol #: AMC-068

NCI Version Date: 03DEC2019
Protocol Date: 03DEC2019

Due to the study closure and participants having completed study therapy, no changes were made in response to the disapproval letters for protocol versions 6 and 7.

I. Scientific and Substantive Changes:

#	Section	Description of Changes
1.	Follow-up after chemotherapy is completed How long will I be in the study?	The follow-up period was changed from 5 years to 2 years as the protocol team believes sufficient data will be collected during the first 2 years of follow-up to complete study analysis.The follow-up period was modified in that participants who have completed study drug therapy and have not progressed will return for office visits to complete required follow-up procedures for to 2 years or until disease progression, whichever comes first. Participants who progress during treatment or follow up will not have to come back for office visits, but may be contacted for health updates for the duration or remainder of the 2 year follow-up.

II. Administrative and Editorial Changes:

#	Section	Description of Changes
2.	Global	Version number and version date were updated to version 8.0 dated 03DEC2019.

MODEL INFORMED CONSENT

AMC-068: Randomized, Phase II Trial of CHOP vs. Oral Chemotherapy with Concomitant Antiretroviral Therapy in Patients with HIV-associated Lymphoma in Sub-Saharan Africa

INTRODUCTION

This is a clinical trial (a type of research study). Clinical trials include only subjects who choose to take part. Before you decide to be a part of this research study, the risks and benefits should be fully explained so that you can make an informed decision. This process is known as informed consent. This consent form provides information about the study and the required tests. Your doctor has also explained this study to you. You will be asked to sign this form if you want to take part. Your decision to take part in the study is voluntary. This means that you are free to choose if you will take part in the study or not. Please take your time to ask questions and make your decision. Discuss it with your friends and family.

You are being asked to take part in this research study because you are infected with human immunodeficiency virus (HIV), the virus that causes AIDS, and have non-Hodgkin's Lymphoma (NHL), a type of cancer associated with AIDS.

This study will take place at 4 hospitals in Africa that are part of the AIDS Malignancy Clinical Trials Consortium (AMC). The AMC is a group of researchers who study cancer treatments for people with HIV infection. The AMC is sponsored by the National Institutes of Health, a part of the U.S. government.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to see if a mixture of anti-cancer medicines given by mouth is as good as a mixture of anti-cancer medicines given by vein for treating Africans with AIDS and NHL. This study will help develop better treatments for people with AIDS and cancer in Africa.

If you take part in this study, you will be given one of two mixtures of anti-cancer medicines. The first mixture contains 4 anti-cancer medicines: cyclophosphamide, doxorubicin, vincristine, and prednisone. This mixture is sometimes called "CHOP", and is a standard treatment for NHL in many parts of the world. However, many African centers have trouble giving this treatment The second mixture also contains 4 anti-cancer medicines: lomustine, etoposide, cyclophosphamide and procarbazine. These medicines have been approved by the United States Food and Drug Administration (FDA) for treating cancer, but they are non-standard (experimental) for treating your type of NHL. They have been given to people with HIV and NHL in several countries, including a small number of Africans with HIV and NHL in Uganda and Kenya. We do not know if taking treatment by mouth or by vein is better. This study will try to find out more about using these two different drug mixtures in people with NHL who are also being treated for HIV.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 90 people will take part in this study.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

Before you begin the study

To be able to join this research study, you need to be at least 18 years old and have a positive blood test for HIV. You must also have had a biopsy (cutting out of a piece of your tissue) that shows you have NHL. Samples of your biopsy must be available for review to be sure that you have NHL. The biopsy will be reviewed by a doctor at the study site and will also be sent to an outside laboratory in the United States for a review of the diagnosis. You must not have received treatment for NHL in the past. You must be willing and able to sign this informed consent.

If you agree to join this study and sign this informed consent, you will need to have *some or all* of the following exams, tests, or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care. They may be done even if you do not join the study. If you have had some of the tests recently, they may not need to be done again.

- A medical history and review of any medications you are taking, including HIV medications
- Physical exam (including neurological exam)
- Vital signs (height, weight, blood pressure, pulse, temperature)
- Blood tests to check your blood cell numbers and how well your liver and kidneys are working. Approximately 10 milliliters (2 small spoonfuls) of blood will be taken from your arm. If there is no copy of a previous positive HIV test available, some of this blood will be used to test for HIV.
- Blood tests to check the effect of HIV on your immune system (the part of the body that fights infections and diseases) and the amount of HIV virus in your blood (viral load)
- Pregnancy test (if you are a woman who could have children). The test results must be negative to take part in this study.
- A test of the fluid that surrounds the brain and spinal cord. A sample of this fluid will be tested to check if you have cancer in your brain or spinal cord or in the fluid around your spinal cord. This test is obtained by lumbar puncture (description of procedure under "Lumbar Puncture: Definition and Risks" below). It is also called a spinal tap.

During the study

If the exams, tests, and procedures show that you can be in the study, and you choose to take part, the following will happen: Patients will be asked to maintain a medication diary and to bring their medication bottles during all future visits.

Tests before you begin treatment

Besides the tests done to find out if you can be in the study, you will be given the following tests and procedures before you begin treatment in the study.

- A chest X-ray, an ultrasound of the abdomen, and CT scans (tests that take pictures) of your chest, abdomen, and pelvis so that your doctor can measure your cancer.
- Bone marrow biopsies to see if you have cancer in the tissue of your bones (description of procedure under "Bone Marrow Examination: Definition and Risks" below).
- If samples of your NHL biopsy are not available for review, you may need to have another biopsy before starting treatment. The biopsy will be reviewed by a doctor at the study site. The tissue sample will also be sent to a laboratory in the United States for more tests to find out more about your NHL.

- Blood tests to check your blood cell numbers and how well your liver and kidneys are working. Approximately 10 milliliters (2 small spoonfuls) of blood will be taken from your arm.
- Pregnancy test (if you are a woman who could have children). The test results must be negative to take part in this study.

If you are not taking medicines to treat your HIV infection, your doctor will prescribe them for you. If you are already taking anti-HIV medications, continue taking them unless your study doctor tells you to change them. You should take all your anti-HIV medications during and after the study, unless your doctor tells you to stop or change them.

Treatment description

A computer program will randomly assign you to one of two treatment arms – this is called randomization. Each participant will be assigned the CHOP treatment group or the lomustine, etoposide, cyclophosphamide and procarbazine treatment group. Your study doctor will tell you which treatment you will receive.

Depending on which anti-cancer medications you are assigned you will be given the medications in one of two ways: roughly half of the patients will be given six (6) cycles of a mixture of medications called CHOP given by vein and prednisone by mouth, with each cycle lasting 21 days. The other half of patients will be given three (3) cycles of a mixture of chemotherapy medicines by mouth, with each cycle lasting 42 days. The total treatment time will be the same in both groups: 126 days or 18 weeks.

Below is an outline of the two combinations of drugs and dosing of the drugs you may receive. Drugs in Table 1 are all given through a vein (by an intravenous catheter) except prednisone which is given by mouth. Your study doctor or nurse will tell you how many prednisone pills to take and when to take them. You will come to the study center to receive these medications on the following days of each cycle:

Table 1: CHOP Given Through Arm Vein

DRUG YOU WILL RECEIVE	DAYS YOU WILL RECEIVE DRUG	CYCLE WHEN DRUG IS TAKEN
Cyclophosphamide	Day 1	Cycles 1 to 6
Doxorubicin	Days 1	Cycles 1 to 6
Vincristine	Day 1	Cycles 1 to 6
Prednisone (by mouth)*	Days 1, 2, 3, 4, 5	Cycles 1 to 6

*Prednisone will be given at the study center on Day 1. Doses on Days 2-5 will be taken at home.

Drugs in Table 2 are given by mouth as pills or capsules. The number of pills or capsules you need to take will depend on your height and weight, and may be changed during your treatment if you have changes in your blood counts. Your study doctor or nurse will tell you how many pills or capsules to take and when to take them. The medications will be taken on the following days of each cycle:

Table 2: Study Medication Taken by Mouth		
DRUG YOU WILL RECEIVE	**DAYS YOU WILL RECEIVE DRUG**	**CYCLE WHEN DRUG IS TAKEN**
Lomustine	Day 1	Cycle 1 and cycle 3 only
Etoposide	Days 1, 2 and 3	Cycles 1, 2, and 3
Cyclophosphamide	Days 22, 23, 24, 25 and 26	Cycles 1, 2, and 3
Procarbazine	Days 22, 23, 24, 25 and 26	Cycles 1, 2, and 3

Tests and procedures

During study drug therapy

During the study, you will also have the following tests or procedures performed while you are receiving study medication therapy:

- Physical exam (on Day 1 of each cycle if receiving IV medications and Day 1 and Day 22 of each cycle if receiving oral medications)
- Vital signs (blood pressure, pulse, temperature, weight)
- Blood tests (on Day 1 of each cycle if receiving IV medications and Day 1 and Day 22 of each cycle if receiving oral medications).
    - Blood tests to check your blood cell numbers and how well your liver and kidneys are working. Approximately 10 milliliters (2 small spoonfuls) of blood will be taken from your arm.
    - Blood tests to check the effect of HIV on your immune system (the part of the body that fights infections and diseases) and the amount of HIV virus in your blood (viral load)
- If you are a woman who could have children, a pregnancy test (on Day 1 of each cycle if receiving IV medications and Day 1 and Day 22 of each cycle if receiving oral medications). The test results must be negative to continue receiving study drug therapy.
- Review of the medicines you are taking, including your HIV medications

At the end of study drug therapy

After you have finished therapy, you will have the following tests or procedures performed:

- Blood tests to check your blood cell numbers and how well your liver and kidneys are working. Approximately 10 milliliters (2 small spoonfuls) of blood will be taken from your arm.
- Blood tests to check the effect of HIV on your immune system (the part of the body that fights infections and diseases) and the amount of HIV virus in your blood (viral load)
- Chest X-ray, sonogram or ultrasound of the abdomen, and CT scan (tests that take pictures) so that your doctor can measure your cancer.
- Bone marrow biopsy, if it is known that you have cancer in the tissue of your bones.

Follow-up after study chemotherapy is completed

- After you finish taking study chemotherapy, you will need to return for office visits 3 months, 6 months, 12 months, 18 months and 24 months later. At these visits, the doctor will do tests to see if your cancer is getting better or worse. At these visits, you may need to have blood collected to check your general health (approximately 10 milliliters or 2 small spoonfuls), chest X-rays, scans, sonograms or ultrasounds done.

HOW LONG WILL I BE IN THE STUDY?

If you join this study, you will be in the study for a total of 2.5 years. For the first 18 weeks, you will be getting treatment for your NHL. After that, you may need to come back for check-ups and tests, or we will follow your health for up to 2 years.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study staff and your regular doctor first.

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.

The study doctor may also need to take you off the study drugs without your permission if:

- Your condition worsens or your doctor believes that further treatment would be of no benefit to you or would be dangerous;
- 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; or
- you are not able to take these drugs as required.
- you become pregnant and/or insist upon breastfeeding

WHAT ARE THE RISKS OF THE STUDY?

You may have side effects from the study medications while on the study. Your doctor and the study team will watch you carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the drugs in this study. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your doctor about any side effects that you have while taking part in the study. It is also possible one of the treatments is better than the other treatment.

Risks of Chemotherapy Drugs used in this study

Chemotherapy drugs often have side effects. Your doctor and the study team will watch you carefully for any side effects. However, doctors don't know all the side effects that may happen. The drugs used in this program may cause all, some or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring which may be life-threatening

or severe enough to cause death. Your health care team may give you medicines to help lessen side effects. You should talk to your doctor about any side effects that you have while taking part in the study.

Doxorubicin

Common side effects:

- Nausea and vomiting
- Temporary hair loss
- Low white blood cell count, which can lead to infection
- Low platelet count, which can lead to bruising or bleeding
- Fatigue (tiredness) and loss of appetite

Rare side effects:

- Heart damage may occur at high doses

Very rare, but serious side effects:

- Liver damage may occur at high doses
- Other cancers, like leukemia (cancer of the blood)

Vincristine

Common side effects:

- Nausea and vomiting
- Temporary hair loss
- Constipation
- Tingling or numbness of the arms or legs
- Fatigue (tiredness) and loss of appetite

Rare side effects:

- Low white blood cell count, which can lead to infection
- Low platelet count, which can lead to bruising or bleeding

Prednisone

Common side effects:

- High blood pressure
- Skin changes (thinning of skin, delayed healing)
- Swelling
- Increased risk of infection
- Thinned bones
- Difficulty sleeping

Rare side effects:

- High blood sugars

Very rare, but serious side effects:

- Worsening of tuberculosis
- Vision changes

Lomustine

Common side effects:

- Low white blood count, which can lead to infection
- Low platelet count, which can lead to bleeding or bruising
- Nausea and vomiting

Rare side effects:

- Mouth sores
- Hair loss
- Confusion
- Drowsiness (feeling sleepy)
- Loss of muscle coordination
- Mild liver damage

Very rare, but very serious side effects:

- Other cancers, like leukemia (cancer of the blood)

Cyclophosphamide *(given by mouth and given by arm vein)*

Common side effects:

- Nausea and vomiting
- Temporary hair loss
- Low white blood cell count, which can lead to infection
- Low platelet count, which can lead to bruising or bleeding
- Fatigue (tiredness) and loss of appetite
- Nasal congestion, watery eyes and headache
- Skin rash; darkening of skin
- Metallic taste in the mouth
- Light-headedness and a hot feeling for a few minutes after taking the drug

Rare side effects:

- Bladder irritation with burning during urination – this may be prevented by drinking 8 to 10 glasses of water a day while on the drug.
- Both men and women may be unable to have children after receiving this chemotherapy. This may be a permanent side effect.
- Women may stop having menstrual periods

Very rare, but serious side effects:

- Scarring of the lungs, cough and shortness of breath
- Liver and heart damage may occur at high doses
- Other cancers, like leukemia (cancer of the blood)

Etoposide

Common side effects:

- Low white blood cell count, which can lead to infection
- Low platelet count, which can lead to bruising or bleeding
- Nausea and Vomiting
- Hair loss
- Fatigue
- Mouth sores

Rare side effects:

- Chest discomfort
- Low blood pressure
- Liver damage
- Allergic reactions

Very rare, but serious side effects:

- Other cancers, especially leukemia (cancer of the blood)

Procarbazine

Common side effects:

- Nausea and Vomiting
- Hair loss
- Diarrhea
- Muscle aches and joint pains
- Rash on the hands and feet
- Fatigue
- Irregular menstrual cycles in women
- Loss of ability to have children
- Severe reactions, including very high blood pressure, chest pain, and heart problems if you also eat cheeses or drink wine, beer, or other alcoholic beverages
- Drowsiness (sleepiness); avoid using sleeping pills, pain medicines or tranquilizers at the same time
- Low white blood cell count, which can lead to infection
- Low platelet counts, which can lead to bruising or bleeding

Rare side effects:

- Loss of muscle coordination
- Depression, confusion, nightmares, hallucinations
- Trouble sleeping

Risk to the Unborn Child and Fertility (Men and Women)

Both men and women will be included in this study. A pregnancy test will be performed at the time of enrollment and if you are pregnant you **will not** be able to participate in this study. The study therapy may decrease your ability to have children. Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You must also not be nursing a baby during this study. When you are taking the study 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 6 weeks after stopping the study drugs. If you are a woman and are unable to use two methods, your doctor will talk with you about your options. 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)
- Not having sex

If you or your partner becomes pregnant while in this study you must tell the study doctor immediately. The doctor will advise you of the possible risks to your unborn baby and discuss your choices for how to proceed. Women who become pregnant or who will not stop breastfeeding during drug treatment will stop receiving treatment for her cancer, but will be asked to continue study visits.

Bone Marrow Biopsy: Definition and Risks

A bone marrow biopsy is the removal of a sample of bone marrow and a small amount of bone (usually from the hip) through a large needle. The doctor will first give an injection of numbing medicine to lessen pain from the test, but you may still have some pain. The pain normally lessens within minutes to hours and may remain as soreness for several days. The doctor will then take two samples of bone marrow, one from each hip bone, using a needle. The doctors at the study center will then look for cancer cells in the bone marrow under a microscope. You must keep the area clean and dry for 24 hours to prevent a small risk of infection or bleeding. This test will be done in the outpatient department.

Lumbar Puncture: Definition and Risks

A lumbar puncture (also called a spinal tap) is a procedure in which a very thin needle is put into the sac of liquid around the lower part of the spine. A small amount of this liquid, which is called cerebrospinal fluid, is collected to look for cancer cells. A lumbar puncture has a small risk of infection, bleeding, nerve damage, or headache. Rarely, leakage of spinal fluid into the tissue can cause a severe headache that lasts for days to weeks. Headache can be treated with paracetamol. You will be given medications to numb the area before the test to prevent pain. The pain usually lasts for a

short time (a minute or two) but sometimes lasts longer. This test will be done in the outpatient department.

Risk of Non-Study Medications

There is a risk of serious and/or life-threatening side effects when certain medications are taken together. 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 medications, vitamins, herbs or other remedies 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.

For more information about risks and side effects, ask your study doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. A possible benefit is that your NHL may shrink or go away. It is also possible that you may receive no direct benefit from being in this study. Information learned from this study may help others who have HIV and NHL.

WHAT OTHER OPTIONS ARE THERE?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- No therapy for your NHL at this time, with care to help you feel more comfortable.

[Insert general information about NHL treatment availability in your country or locale]

Talk to your doctor or clinic staff about other treatment choices in your area and the risks and the benefits of all the choices before you decide if you will take part in this study.

WHAT ABOUT CONFIDENTIALITY?

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. Any publication of this study will not use your name or identify you personally.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as trained staff at [*Your Institution's Name*], your country's national health agency, the Office for Human Research Protections (OHRP), and trained staff from the AIDS Malignancy Clinical Trials Consortium (AMC), the National Cancer Institute (NCI), and the AMC Operations and Data Management Center (Data Coordinators and Study Monitors), the pharmaceutical collaborator(s) (Sigma Tau and Mylan).

The NIH has given the AMC a Certificate of Confidentiality. The Certificate does not mean that the NIH or the U.S. Government recommend that you take part in this study. This Certificate helps us keep your health information private.

Your records for this study will have information that may identify you. This Certificate lets us turn down legal demands for your study records. We can use the Certificate to turn down demands for records from a U.S. court. The Certificate can be used in any federal, state, or local legal matters. We will use the Certificate to turn down any demands for your study records. The cases where we cannot use the Certificate are explained below.

We cannot use the Certificate to say no a demand from the U.S. Government for study records. This applies to audits or reviews of the AMC. This also applies to study records that we have to report to the FDA.

The Certificate does not stop you or your family members from sharing your health information. It does not stop you from talking about taking part in this study. You may give written permission for an insurer, employer, or other person to get copies of your study records. If you give permission, we cannot use the Certificate to say no to a request for your study records.

The Certificate cannot be used to turn down legal demands outside of the U.S.

WHAT ARE THE COSTS?

There will be no cost to you for study-related visits, physical examinations, laboratory tests or other procedures. *(Modify the prior statement to local requirements if subjects will be expected to cover the cost of any research-related care, tests, or supplies.)* You, your insurance company, or your health care system will need to assume the cost of anti-HIV drugs, which are 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.)*

The study therapy you will receive if you take part in this study is being supplied by the AIDS Malignancy Consortium at no cost to you.

You will receive no payment for taking part in this study. *(insert information about help with transportation to and from study visits, if any).*

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. No funds have been set aside for any treatment for injuries, 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 PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part in this study or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

WHAT IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- *(name & telephone number for the investigator or other study staff)*

For questions about your rights as a volunteer 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)*

A description of this clinical trial will be available on http://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.

SIGNATURE

I have been given a copy of this form. I have read it or it has been read to me. All of my questions have been answered to my satisfaction. I agree to participate in the clinical trial.

Participant's Name (print)	Participant's Signature and Date
Witness's Name (print) (As appropriate)	Witness's Signature and Date

I have fully explained this research study to the subject or guardian. In my judgment, there was sufficient access to information, including risks and benefits, to make an informed decision.

Investigator Obtaining Consent Name (print)

Investigator Obtaining Consent Signature and Date