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STUDY TITLE: Short-Course EPOCH-Rituximab for Untreated CD-20+ HIV-Associated Lymphomas

STUDY SITE: NIH Clinical Center

Cohort: Standard

Consent Version: 03/17/2021

WHO DO YOU CONTACT ABOUT THIS STUDY?

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This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

If the individual being asked to participate in this research study is not able to give consent for themselves, you, as the Legally Authorized Representative, will be their decision-maker and you are being asked to give permission for this person to be in this study. For the remainder of this document, the term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

The major purpose of this research study is to determine if the experimental combination of chemotherapy drugs given to you through your veins can lead to disappearance of lymphoma (by our best ability to test for it) within as few cycles as possible, and to see if the lymphoma will

continue to stay undetectable for at least one year if the treatment is stopped one cycle after you enter remission.

WHY ARE YOU BEING ASKED TO TAKE PART IN THIS STUDY?

You have a cancer called non-Hodgkin's lymphoma (NHL) and you are also infected with the human immunodeficiency virus (HIV). In patients like yourself, the lymphoma often grows and spreads rapidly so chemotherapy is usually used for treatment. Chemotherapy will be discussed in more detail later in this document.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 80 people will take part in this study.

DESCRIPTION OF RESEARCH STUDY

The HIV infection has damaged your immune system, and chemotherapy probably causes further damage to your immune system. If it were possible to limit the amount of immune damage due to chemotherapy, this might decrease the number of infections and decrease the risk of developing cancer in the future. This research protocol is designed to help answer whether it may be possible to limit the amount of damage chemotherapy causes to the immune system by reducing the total amount of chemotherapy given. However, if too little chemotherapy is given, then the cancer will not be cured. In this research protocol, we will administer a combination of drugs for lymphoma and perform sensitive tests to see if all evidence of your cancer goes away very early in the course of your treatment. If the cancer goes away quickly, then the treatment will be stopped after 9 weeks of therapy. If your cancer continues to be evident, you will receive up to 18 weeks of treatment. The standard treatment for your type of cancer is usually given for 18 to 24 weeks. We will also monitor your immune system to see how much immune damage occurs with the treatment. After you finish treatment, we will monitor your immune system to see if it improves or not, and we will look for evidence of the cancer coming back.

WHAT WILL HAPPEN IF YOU TAKE PART IN THIS RESEARCH STUDY?

None of the drugs in this treatment are experimental. The United States Food and Drug Administration has approved all of the drugs for use in lymphoma. However, as explained below, the way the drugs in this research protocol are given in combination together is experimental.

In addition to receiving chemotherapy into your veins, you will also receive chemotherapy directly into your spinal fluid using a procedure called lumbar puncture (explained in the next paragraph). This part of the therapy is not experimental. The spinal fluid bathes the brain and spinal cord and is separated from the rest of your body fluids by tissue that prevents the chemotherapy drugs given by vein from getting into the spinal fluid. It is important to get the chemotherapy into the spinal fluid because in AIDS-lymphoma, the spinal fluid and brain frequently get lymphoma in them. The chemotherapy must therefore be given by lumbar puncture or some other method to get it directly into the spinal fluid. We will test to see whether there is any evidence of lymphoma in your brain or spinal fluid before deciding how to treat the spinal fluid. If there is no evidence that the lymphoma has gotten into your brain or spinal fluid, you will receive the chemotherapy into the spinal fluid twice weekly every third week for 6 doses. If there is evidence of brain or spinal fluid lymphoma, then you will receive up to 3 drugs simultaneously into the spinal fluid. These treatments will be given twice weekly for at least 4 weeks, and will continue for once weekly for

at least 4 more weeks, and then once monthly for at least 6 more treatments. Sometimes it is necessary to have the neurosurgeons perform an operation to place a device called an Ommaya into your head that the chemotherapy is given through if the lumbar punctures are not feasible. If you need an Ommaya, you will be consented separately for that. Additionally, you may require radiation therapy to your head and spine. As stated above, this part of the therapy is not experimental, and will be determined on the basis of your individual medical needs. Even though this part of the therapy is not experimental, it is required as part of the research protocol.

BEFORE YOU BEGIN THE STUDY

Prior to getting any treatment, there are a number of tests that must be completed. As reviewed in the paragraph above, you will undergo a lumbar puncture to remove a small amount of spinal fluid (about 1-2 teaspoons) that will be tested for the presence of lymphoma cells. A lumbar puncture is done by inserting a small sterile needle through the skin and muscle, going between the bones of the spine in the lower back until the needle punctures the spinal canal covering. The spinal fluid will then drain out through the needle on its own.

Other tests that you will have done include either a computed tomogram (CAT Scan) of the head, or an MRI of the head. These tests help to see if there are any tumors growing in the brain tissue. CAT scans will also be done of your chest, abdomen, and pelvis. This will help to see if there are any tumors in these parts of your body. Another test to help determine whether lymphoma is present is a positron emission tomography scan (PET scan). This scan is accomplished by injecting a kind of glucose into your blood, and the scanning machine can measure how different cells in the body use it. This can help determine where the lymphoma is, because the lymphoma cells use the glucose differently from other types of cells. Another procedure required is called a bone marrow biopsy. This procedure is done by inserting a small hollow needle through the bone, usually in the back of the pelvis bone, to get some of the bone marrow. The bone marrow is then inspected for evidence of lymphoma. You will also have an Electrocardiogram (ECG) which is a test that is performed while you lie still for about 5 minutes. It involves placing electrodes (small stickers that are attached to wires that go to the machine) on your chest and arms/legs and recording the electrical activity of your heart.

During the study

EPOCH-R Chemotherapy

The chemotherapy you will receive on this experimental protocol is called EPOCH-R. Each letter in this name stands for the name of a drug that is part of the chemotherapy regimen. The individual drugs will be discussed below. EPOCH-R is different from standard chemotherapy because some drugs are administered over a 4-day period (96-hours) instead of over several hours. Experimental studies in patients with AIDS-lymphoma and in lymphoma without HIV infection suggest that administering some drugs over a 4-day (96 hours) period may increase their effectiveness and reduce toxicity. Although EPOCH-R is a combination of 6 non-experimental drugs, the way the drugs are used is experimental in AIDS-related lymphoma. Rituximab is a monoclonal antibody (a protein that specifically binds to proteins that occur on the surface of lymphoma cells). When rituximab attaches to these cell surface proteins, it may cause the lymphoma cells to die, or make them more sensitive to EPOCH. The Food and Drug Administration has approved rituximab for use in a type of lymphoma that is not HIV-associated. Rituximab is not an experimental drug. The use of rituximab with EPOCH in AIDS is experimental. There is a theoretical possibility that

EPOCH with rituximab can worsen your immune function, because rituximab decreases the number of B-lymphocytes in your body. B-lymphocytes are important in that they produce antibodies that are important in certain kinds of infections. Therefore, rituximab could make you more prone to bacterial and other infections. The rationale for using the rituximab with EPOCH is to see if there is evidence that combining these therapies is tolerated or not, and to see if it appears to improve the effect of the EPOCH against the lymphoma so that fewer than the standard number of cycles of standard therapy can be administered. The rituximab will be administered twice during each treatment cycle: first immediately before the other drugs are given, and second, at the end of the 96 hours right before the cyclophosphamide is given. It may take several hours to give the rituximab because if it is infused too quickly it can make you feel ill (headache, shortness of breath, rash).

You will receive three of the drugs, etoposide, doxorubicin and vincristine, over 4 days (days 1 to 5) through a catheter placed in a large vein. A portable pump that you will carry around with you will infuse the drugs. You do not need to be hospitalized for this therapy but you will have to come to the clinic every day to have the chemotherapy replaced in the pumps. You will also take prednisone by mouth on days 1 through 5, and on day 5, you will receive cyclophosphamide by intravenous injection (the drug will be injected directly into the vein with a needle or catheter) over approximately 30 minutes. The doses of chemotherapy will be adjusted, based on how well you tolerate the therapy. Because chemotherapy damages your bone marrow, you will receive a non-experimental drug called filgrastim (also called granulocyte-colony stimulating factor or G-CSF), which helps stimulate bone marrow function. You will receive this for approximately two weeks, beginning on the sixth day of therapy. The nurses will teach you to administer the filgrastim as a daily injection just under the skin (like an insulin shot).

You will receive as few as three cycles and a maximum of six cycles of EPOCH-R chemotherapy. Each cycle is repeated every 3 weeks, although a cycle may be delayed for medical reasons. The size of your tumors will be evaluated with computerized tomography (CT) scans, and PET scans before you start treatment. These scans will be repeated after you have completed the 2nd through 6th cycles of EPOCH-R. You will receive one additional cycle of treatment past when it appears that your tumor has completely responded to treatment: therefore, you may receive as few as 3 cycles of chemotherapy.

Treatment will be stopped if the tumor is growing or if you are unable to safely tolerate the therapy.

Supportive Therapy

Because chemotherapy can lower your resistance to infection, you will receive preventative therapy for a kind of pneumonia called Pneumocystis carinii with a drug called trimethoprim/sulfamethoxazole (Bactrim®). This is administered three times a week during the time you receive EPOCH and rituximab. If you are allergic to Bactrim or cannot tolerate it, you may receive an alternative therapy. If you need prophylaxis or treatment for other AIDS-related infections such as fungal infections (like thrush), mycobacterium avium complex (MAC), tuberculosis (TB), toxoplasmosis, cryptosporidium, or cytomegalovirus, those medications may have to be stopped during the EPOCH infusions to avoid potentially harmful drug interactions.

While you are being treated with EPOCH, the intent is that your anti-HIV drugs will be continued. These drugs may inhibit your bone marrow function or interact with the chemotherapy to cause

other or increased side effects. However, it has been shown that continuing anti-retroviral drugs may be important for your overall treatment.

Samples for Research
Blood samples will be collected for research studies to look at the response of HIV and the cancer to the treatment. These will be collected prior to and after each cycle of treatment (up to 4 tablespoons each time), and after treatment at about 2 months, every 3 months for 1 year, and every 6 months for an additional year (up to 4 tablespoons each time). In addition, portions of tissue collected as part of other, routine procedures that you may have had in the past or in the future for your disease will also be collected for research studies.

Optional Blood Collection for Research
You may be asked to donate a small amount of blood for research. If you agree to this, you will have up to 7 tablespoons of blood collected up to 4 times after you complete treatment.

The blood collected is exclusively for research purposes and will not benefit you. It might help other people in the future. The decision to participate in this part of the research is optional, and no matter what you decide to do, it will not affect your care.

If you agree to the optional blood samples, your agreement will be documented in the records.

What tests will be done on my samples?
Your blood and tissue that is collected will be used to look for specific changes in the DNA in tumors that could be used to develop new ways of diagnosing and treating cancer, and to understand more about HIV. DNA (also called deoxyribonucleic acid) are the molecules inside cells that carry genetic information and pass it from one generation of cells to the next – like an instruction manual. Normal tissue contains the DNA (instructions) that you were born with, DNA in tumor cells has changed – or mutated – and we think that change in the DNA is what causes tumors to form and to grow, forming the cancer genome or DNA. In order to determine which parts of the DNA have mutated, we will compare the DNA in your tumor cells to DNA from your normal cells. When we are examining these pieces of your DNA, it is possible that we could identify possible changes in other parts of your DNA that are not related to this research. These are known as "incidental medical findings".

These include:

- Changes in genes that are related to diseases other than cancer
- Changes in genes that are not known to cause any disease. These are known as normal variations.
- Changes in genes that are new and of uncertain clinical importance. This means that we do not know if they could cause or contribute to a disease or if they are normal variations.

However, the analyses that we perform in our laboratory are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing. Changes that we observe unrelated to our research may or may not be valid. Therefore, we do not plan to inform you of the results of testing on your tissue and blood that is performed in our research lab. However, in the unlikely event that we discover a finding believed to be clinically important based on medical standards at the time we first analyze your results, we will contact you. This could be many years in the future. We will ask you to have an additional

tube of blood drawn to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and offered the opportunity to come to NIH to have genetic education and counseling to explain this result; at the time of any such event(s), these activities will be paid for by the NCI. If you do not want to come to NIH a referral to a genetic healthcare provider will be provided to discuss the results (at your expense).

Who else besides the investigators on this study will know the results of my sample testing?

Once we obtain any of the samples listed above, the investigators take all your personal information off those samples and label them with a study code number. Only the investigators on this study know who the sample came from. The key linking your personal information with the code number is kept in a secure computer data base, with access only to key research staff who will be discussing this study with you. Once the sample has been labeled with a code, it is sent to a variety of NIH laboratories for storage and testing. No one testing your samples will be able to link the results to you personally. Specimens obtained during your participation in this study may be sent for testing to investigators outside of NCI or the NIH. All samples will be coded to protect your privacy and no personal information will be included. Other investigators on this study will have access to limited clinical and biologic data such as age, gender and disease status.

How long will your samples be stored?

The samples collected during this study will be stored for as long as the study is open. When this study is closed, we will keep the samples for future research.

When you are finished taking the drugs (treatment)

If your disease does not enter remission or it recurs, you may need further therapy. If no protocols are available for the treatment of your disease, you will be returned to the care of your local physician. It is important to stress that participation in this protocol does not constitute a promise of long-term medical care at the Clinical Center.

BIRTH CONTROL

Because it is possible that drugs in EPOCH-R can affect a developing fetus, and because you can transmit HIV to your sexual partner, you will be asked to practice an effective method of barrier birth control and safe sex while you are participating in this study.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Because of the danger of HIV infection with the exchange of body fluids, all participants in this study must agree to safe sex practices and to use condoms while engaging in sexual intercourse.

RISKS OR DISCOMFORTS OF PARTICIPATION

What side effects or risks can I expect from being in this study?

Your physicians will watch you closely for these side effects and will stop treatment if any side effects become a serious threat to your life or wellbeing. Your physicians will also stop the treatments if it becomes clear that the treatment is not successfully controlling your disease.

There are unforeseeable risks whenever investigational treatment programs are undertaken, including death. Chemotherapy has the potential of causing a rapid acceleration of HIV disease and increasing the chances of developing opportunistic infections with viruses, parasites or fungi. Your doctors will monitor you carefully for these complications. If they should become a threat to your health and it is considered dangerous to proceed with the investigational treatment protocol, you will be removed from the study. If you have complications of therapy, you will be evaluated and appropriately treated for any acute effects of treatment. In the event of emergency medical needs, referral to the closest facility is mandatory, and NIH cannot reimburse for those costs.

Risks and side effects related to the treatment and the procedures on this study are identified below:

EPOCH-R

The drugs used in EPOCH-R are not experimental. This chemotherapy regimen can cause severe fatigue. It can also cause you to have abnormal lab values, most of which cause no symptoms and do not require treatment. Side effects that have been observed with the drugs in this program when they are used individually include the following:

Doxorubicin:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Doxorubicin, more than 20 and up to 100 may have:
• Hair loss • Vomiting • Red colored urine, saliva, or sweat

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Doxorubicin, from 4 to 20 may have:
• Heart failure or heart attack which may cause shortness of breath, swelling of ankles, cough or tiredness which may occur years after the dose • Abnormal heartbeat • Cancer of the bone marrow (leukemia) caused by chemotherapy • Damage to the lungs which may cause shortness of breath when combined with radiation • Infection, especially when white blood cell count is low • Bruising, bleeding • Anemia which may cause tiredness, or may require transfusion • Hepatitis or damage to the liver which may cause yellowing of eyes and skin, swelling • Kidney damage which may require dialysis • Sores in the mouth or throat • Belly pain • Nausea, diarrhea • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Damage to the skin which may cause pain • Swelling and redness at the site of the medication injection or area of previous radiation • Loss of nails • Darkening of the nail beds or skin or hands and feet

RARE, AND SERIOUS In 100 people receiving Doxorubicin, 3 or fewer may have:
• Severe blood infection

Cyclophosphamide:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, more than 20 and up to 100 may have:
• Hair loss, skin changes, rash, change in nails • Nausea, vomiting, diarrhea, loss of appetite, pain in belly • Sores in mouth • Infection, especially when white blood cell count is low • Absence of menstrual period which may decrease the ability to have children • Blood in urine

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, from 4 to 20 may have:
• Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Loss or absence of sperm which may lead to an inability to father children • Stuffy nose • Scarring of the lungs which may cause shortness of breath • Fluid around the heart

RARE, AND SERIOUS In 100 people receiving Cyclophosphamide, 3 or fewer may have:
• Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Damage to the heart or heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness • A new cancer including cancer of bone marrow (leukemia) caused by chemotherapy • Swelling of the body including the brain which may cause dizziness, confusion

Prednisone:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Prednisone, more than 20 and up to 100 may have:
• High blood pressure which may cause headaches, dizziness, blurred vision • Pain in belly • Loss of bone tissue • Mood swings • In children and adolescents: decreased height • Swelling of the body, tiredness, bruising • Increased appetite and weight gain in the belly, face, back and shoulders • Difficulty sleeping • Skin changes, acne

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Prednisone, from 4 to 20 may have:
• Blood clot which may cause swelling, pain, shortness of breath • Infection • Kidney stones • Diabetes • Glaucoma • Cloudiness of the eye, visual disturbances, blurred vision • A tear or a hole in the bowels which may cause belly pain or that may require surgery • Heartburn • Damage to the bone which may cause joint pain and loss of motion • Numbness and tingling of the arms, legs and upper body • Muscle weakness • Non-healing wound

RARE, AND SERIOUS In 100 people receiving Prednisone, 3 or fewer may have:
• Bleeding from sores in the stomach • Broken bones

Hydrocortisone:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Hydrocortisone, more than 20 and up to 100 may have:
• High blood pressure • Damage to the bone which may cause joint pain or loss of motion • State of mind that involves a "loss of contact with reality"

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Hydrocortisone, from 4 to 20 may have:
• Diabetes • Swelling of the body and weight gain, tiredness, bruising • Glaucoma • Cloudiness of the eye, visual disturbances • Abnormal menstrual period • Facial hair growth in women

RARE, AND SERIOUS In 100 people receiving Hydrocortisone, 3 or fewer may have:
• None

Dexamethasone:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Dexamethasone, more than 20 and up to 100 may have:
• High blood pressure which may cause headaches, dizziness • Pain in belly • Infection • Diabetes • Loss of bone tissue • Damage to the bone which may cause joint pain or loss of motion • Mood swings • In children and adolescents: decreased height • Swelling of the body, tiredness, bruising • Increased appetite and weight gain in belly, face, back and shoulders • Difficulty sleeping • Skin changes, rash, acne

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Dexamethasone, from 4 to 20 may have:
• Blood clot which may cause swelling, pain, shortness of breath • Kidney stones • Glaucoma • Cloudiness of the eye, visual disturbances, blurred vision • A tear or a hole in the bowels which may cause pain or that may require surgery • Heartburn • Numbness and tingling of the arms, legs and upper body • Muscle weakness • Non-healing wound

RARE, AND SERIOUS In 100 people receiving Dexamethasone, 3 or fewer may have:
• Bleeding from sores in stomach • Broken bones

Vincristine:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Vincristine, more than 20 and up to 100 may have:
• Constipation, nausea, vomiting • Hair loss • Pain or redness at the site of injection • Numbness and tingling of fingers or toes • Headache, jaw pain and/or muscle pain • Weakness and difficulty walking • Swelling of lower legs

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Vincristine, from 4 to 20 may have:
• Swelling that may be accompanied by confusion, and dizziness • Paralysis, weakness, headache, confusion • Hoarseness • Drooping eyelids • Visual loss • Difficulty with balance and hearing

RARE, AND SERIOUS In 100 people receiving Vincristine, 3 or fewer may have:
• Seizure

Etoposide:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Etoposide, more than 20 and up to 100 may have:
• Infection, especially when white blood cell count is low • Anemia which may require transfusion • Bruising, bleeding • Sores in mouth which may cause difficulty swallowing • Diarrhea, loss of appetite, nausea, vomiting • Tiredness • Fever • Chills • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Etoposide, from 4 to 20 may have:
• Heart failure or heart attack which may cause chest pain, shortness of breath, swelling of ankles, and tiredness • Liver damage which may cause yellowing of eyes and skin, swelling • Severe skin rash with blisters and peeling which can involve inside of mouth and other parts of the body

RARE, AND SERIOUS In 100 people receiving Etoposide, 3 or fewer may have:
• Cancer of bone marrow caused by chemotherapy • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

Rituximab (Rituxan):

COMMON, SOME MAY BE SERIOUS In 100 people receiving Rituximab, more than 20 and up to 100 may have:
• Nausea • Chills, fever • Reaction during or following infusion of the drug • Infection, especially when white blood cell count is low • Anemia which may require blood transfusions • Numbness and tingling of the arms and legs • Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Rituximab, from 4 to 20 may have:
• Bruising, bleeding • Abnormal heartbeat • Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Sores in eye • A tear or a hole in the bowels that may require surgery • Diarrhea, vomiting • Pain • Swelling of the body • Hepatitis, or liver damage which may cause yellow eyes and skin • Dizziness, headache • Kidney damage which may require dialysis • Cough • Scarring of the lungs • Stuffy nose • Blockage of internal organs which may cause shortness of breath, wheezing, vomiting • Increased sweating • Itching, rash, blisters on the skin • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Low blood pressure which may cause feeling faint

RARE, AND SERIOUS In 100 people receiving Rituximab, 3 or fewer may have:
• Damage to the brain caused by a virus which may result in tiredness, weakness, changes in thinking, and disability. This is called progressive multifocal leukoencephalopathy (PML). • Heart stops beating

Filgrastim:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Filgrastim, more than 20 and up to 100 may have:
• Nose bleed • Anemia which may require transfusion • Pain • Diarrhea • Fever • Tiredness • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Filgrastim, from 4 to 20 may have:
• Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of ankles • Damage to the lungs which may cause shortness of breath • Internal bleeding which may cause coughing up blood • Cough • Swelling or tenderness of vessels • Headache

RARE, AND SERIOUS In 100 people receiving Filgrastim, 3 or fewer may have:
• Rupture of the spleen causing sudden or severe pain in the left side of abdomen spreading up to your shoulder

Other risks

- There is also the possible side effect of significant nerve damage, that may result in weakness in the extremities, including in one or both legs (also called "peripheral motor neuropathy"). This is a rare, but possible risk of intrathecal therapy, including with cytarabine and methotrexate, and has been seen on this study.
- It is important to emphasize that when you have a decreased white blood cell count following chemotherapy, you are at high risk of developing an infection. Such infections may be very serious and cause death if not quickly and properly treated. Therefore, if you have a temperature greater than 38.3°C (101°F), you must call your doctor immediately.
- Chemotherapy may also cause your platelets to fall; since platelets are the blood elements that permit blood to clot, this may place you at increased risk of serious bleeding. It may be necessary to give you transfusions of platelets if your platelet counts reach very low levels.
- There is a small chance that damage to the normal bone marrow may eventually result in bone marrow failure, leading to a serious shortage of one or more kinds of cells in the blood, leukemia and death.
- Many of the drugs used in this treatment program are toxic to the egg cells in the ovary and sperm cells in the testicle and may produce sterility. Recovery of normal fertility, although theoretically possible, is very uncertain.

Risks associated with the study procedures:

To determine if this research study is suitable for you, a number of tests need to be done. This period of evaluation may take up to two weeks and if possible will be done on an outpatient basis. These may include blood and urine tests, Computerized tomography (CT) or magnetic resonance imaging (MRI) scans, radioisotope scans, glucose uptake scans, ECG and biopsies of tumor tissue and bone marrow, and a spinal tap (removal of a small amount spinal fluid from the spinal canal by inserting a needle into the lower back). Over the course of this study, approximately one pint of blood will be taken.

- The risks associated with bone marrow biopsies include local pain, bleeding, and infection.
- The risks associated with a spinal tap also include pain, bleeding, and local infection. Under very rare circumstances, brain damage can occur, causing death. This only occurs if there is a large brain mass or tumor causing pressure, and for this reason, we will obtain a brain scan if there is any suspicion that you have a brain tumor.
- The risks of radiation related to FDG and CT scans are described below. In addition to those radiation risks, CT scans that employ contrast may cause allergic reactions, injection site reactions abdominal discomfort and fainting. MRIs carry no radiation risks but are contraindicated in participants with metal in their bodies. In patients that receive gadolinium contrast with MRIs, allergic reactions, injection site reactions and kidney damage may occur.

- The risk related to blood sampling include pain and bruising, lightheadedness, and rarely, fainting.

It is important to obtain fresh biopsies of tumor tissue, even if you already had a biopsy before coming to the NIH. This is done to both confirm the diagnosis and for research purposes. If you have a biopsy done, we will collect portions of it for the research study as it will help us understand why AIDS-related lymphomas are difficult to treat. Biopsies requiring major surgery (e.g. in the chest or the abdomen) will not be performed for research purposes alone but only if necessary for your medical care. Risks of biopsies include pain, bleeding, infection, and the risks to the particular area undergoing surgery. General anesthesia itself is generally safe but has a very small risk of major complications such as heart attack or stroke. The risks of general anesthesia will be explained to you in more detail at the time of surgery if it is needed. Blood samples, other body fluids and tissues that are obtained during testing, operative procedures, or other standard medical practices will also be used for research purposes.

In order to receive EPOCH-R, you will need to have a catheter placed in a large vein. This catheter can be placed in the arm, neck, chest or groin areas. In general, the chest, neck or arm is preferred. For most people, the safest catheters are placed temporarily and removed after each chemotherapy treatment. For some patients, semi-permanent catheters are preferable. These catheters stay in place until all cycles of therapy are completed. While they may seem more convenient, they are associated with a more frequent occurrence of complications. The risks associated with insertion of catheters include pain, bleeding, infection, and puncture of the lung. A lung puncture can result in lung collapse, which might require insertion of a tube into the chest cavity (usually for a day or two) to help the lung reinflate. The long-term risks of catheters include infection and clotting of the vein, and this is more common with semi-permanent catheters. If side effects occur, it may be necessary to remove the catheter, and to treat the infection and/or clot with medication. These risks will be explained to you in more detail at the time of the catheter insertion. You will be advised witch catheter type is likely to be best for you. The catheter type that is best for you may change over the course of therapy.

What are the risks of radiation from being in this study?

During your participation in this research study, you may be exposed to radiation from CTs of the Chest, Abdomen and Pelvis and PET scans each year. The amount of radiation exposure from these procedures is equal to approximately 17.1 rem. A rem is a unit of absorbed radiation.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called “background radiation.” This study will expose you to more radiation than you get from everyday background radiation. No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The CT and PET scans that you get in this study will expose you to roughly the same amount of radiation as 57 years’ worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from

the radiation exposure in this study is 1.7 out of 100 (1.7%) and of getting a fatal cancer is 0.9 out of 100 (0.9%)

You may not participate in this study if you are pregnant. If you are able to become pregnant, we will perform a pregnancy test before exposing you to radiation. You must tell us if you may have become pregnant within the previous 14 days because the pregnancy test is unreliable during that time.

Drugs used in the spinal fluid for lymphoma:

- Methotrexate, when administered into the spinal fluid, may cause low blood counts and ulcerations in the mouth, stomach, and intestines. It can cause acute headache, back pain, stiff neck, and /or fever; it can also cause weakness or paralysis of certain muscles. It can cause seizures and coma. Other side effects it can cause are usually associated with intravenous administration rather than intrathecal (lumbar puncture administration), but these include liver function abnormalities, inflammation and scarring of the lungs, inflammation of the tissue covering the heart, and severe skin reactions. This drug can rarely cause damage to the lungs.
- Leucovorin is related to the vitamin folic acid. For the most part, it is nontoxic in therapeutic doses. However, severe allergic reactions have been reported, but these are rare. It is used to decrease the side effects of the methotrexate.
- Cytosine Arabinoside given my lumber puncture can cause nausea, vomiting, fever, and headaches. Rarely, it can cause weakness and seizures. When given into the spinal fluid, it does not usually cause systemic toxicity, but we will monitor you for low blood counts, and liver function abnormalities, which can occur with cytosine arabinoside when given by vein.

Other risks:

As a patient-volunteer, you may experience considerable psychological stress. This study requires a substantial time commitment over a 2-year period with requirements for blood tests, x-ray's, drug administration, and physician appointments. There is also uncertainty regarding the ultimate outcome of your treatment. Some patients will feel worse, for at least some period during the investigational treatment period, than they did before treatment. Patient-volunteers are encouraged to discuss their feelings with staff members. Your treating physicians, in concert with other members of the treatment team, wish to identify any problems that are affecting your emotional wellbeing, and to help you deal with them. Should you experience sad or disturbing feelings, we have counselors available, and you should notify a member of the treatment team so that arrangements can be made for counseling if you wish it.

Psychological or Social Risks Associated with Loss of Privacy

The following general points are indirectly related to your participation in the research study:

1. Unanticipated medical information: During the course of this investigation, it is possible (although not likely) that we will obtain unanticipated information about your health or genetic background.

2. Release of genetic information:

- Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all of the safety measures that we will use, we cannot guarantee that your identity will never become known. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them.
- While the controlled-access databases developed for this project will not contain information that is traditionally used to identify you, such as your name, address, telephone number, or social security number, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a blood relative) in another database and be able to identify you (or your blood relative). It also is possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information to you.
- Since some genetic variations can help to predict the future health problems of you and your relatives, this information might be of interest to health providers, life insurance companies, and others. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives. Therefore, your genetic information potentially could be used in ways that could cause you or your family distress, such as by revealing that you (or a blood relative) carry a genetic disease.
- There also may be other privacy risks that we have not foreseen.

Protections against misuse of genetic information

This study involves genetic testing on samples. Some genetic information can help predict future health problems of you and your family and this information might be of interest to your employers or insurers. The Genetic Information Nondiscrimination Act (GINA) is a federal law that prohibits plans and health insurers from requesting genetic information or using genetic information. It also prohibits employment discrimination based on your health information. However, GINA does not address discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed condition or disease that has a genetic component.

POTENTIAL BENEFITS OF PARTICIPATION

Are there benefits to taking part in this study?

As a result of participating in this investigational treatment program, you will receive evaluation and treatment of your lymphoma and AIDS. All of the medications, tests, hospitalizations and physician services at the NIH will be free of charge to you. As information is gathered from this trial, results will be shared with you (of course information regarding other patients will never

include the patients name or any other identifying information, to insure patient confidentiality). Although the EPOCH-R chemotherapy is experimental, all of the drugs in EPOCH-R except the rituximab are contained in standard treatment regimens for HIV-related lymphomas. Moreover, we have tested EPOCH alone in AIDS-lymphoma, and it appears to be safe and effective. However, we cannot be certain if you will be cured of your lymphoma and it is possible your tumor may be resistant to chemotherapy, and if this occurs, you may not receive any benefit from this treatment.

ALTERNATIVE APPROACHES OR TREATMENTS

Alternative treatments for AIDS-lymphoma include:

- Standard combination chemotherapy regimens. These are sometimes given in lower than standard doses along with antiretroviral therapy.
- Treatment with single chemotherapy drugs. Therapy with single drugs is better tolerated than combination therapy, and often produce shrinkage of tumor. However, they rarely cure lymphomas.
- Radiation (X-ray) treatments. Tumor growth can be stopped in the areas that receive radiation, but it cannot control disease that has spread to multiple areas because the whole body cannot be irradiated without extreme toxicity.
- Surgery can successfully remove tumors. However, removal of a tumor by surgery rarely if ever cures lymphoma because the tumors have spread to multiple areas.
- Occasionally, patients do not want therapy unless the tumor is causing problems. However, AIDS-related lymphomas are almost always aggressive and will quickly cause symptoms unless treated. Some patients may feel that chemotherapy is not the best approach for them and may wish to have comfort care only. These are issues that should be discussed with your physicians.

STOPPING THERAPY

Your doctor may decide to take you off this study for the following reasons:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you have side effects from the treatment that are your doctor thinks are too severe
- if new information shows that another treatment would be better for you
- if you do not follow the study requirements (for instance, if you are not coming for your study visits when scheduled).

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines,

information collected on you up until that point may still be provided to designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases **cannot** be recalled and destroyed.

CONFLICT OF INTEREST

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

USE OF SPECIMENS AND DATA FOR FUTURE RESEARCH

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect, use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used.

Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future. If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

Genomic Data Sharing

As part of this research study, we will put your genomic data in a large database for broad sharing with the research community. These databases are commonly called data repositories. The information in this database will include but is not limited to genetic information, race and ethnicity, and sex. If your individual data are placed in one of these repositories, they will be labeled with a code and not with your name or other information that could be used to easily identify you, and only qualified researchers will be able to access them. These researchers must

receive prior approval from individuals or committees with authority to determine whether these researchers can access the data.

NIH policies require that genomic data be placed in a repository for sharing. Therefore, we cannot offer you a choice of whether your data will be shared. If you do not wish to have your data placed in a repository, you should not enroll in this study.

PAYMENT

Will you receive any type of payment for taking part in this study?

You will not receive any payment for taking part in this study.

REIMBURSEMENT

Will you receive reimbursement or direct payment by NIH as part of your participation?

On this study, the NCI will reimburse the cost for some of your expenses such as those for hotel, travel, meals. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy. You will be given a summary of the policy which provides more information.

If your travel to the NIH Clinical Center (e.g. flight, hotel) is arranged and paid for by the NIH, the agency making the reservations and their representatives will have access to your identifiable information.

COSTS

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- Some of the specimens and/or data obtained may be sent to researchers outside of the National Cancer Institute to perform additional research studies designed to help us better understand lymphoma.

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;

4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dr. Mark Roschewski, Email: Mark.Roschewski@nih.gov, Telephone number: 240-760-6183. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness to the oral short-form consent process only:

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.