INSTITUTE: National Cancer Institute

STUDY NUMBER: 06-C-0051 PRINCIPAL INVESTIGATOR: Robert Yarchoan, MD

STUDY TITLE: AIDS-related Primary Central Nervous System Lymphoma: A Phase II Pilot Study of High-Dose Intravenous Methotrexate with Rituximab, Leucovorin Rescue and Highly Active Antiretroviral Therapy

Continuing Review Approved by the IRB on 06/26/17

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Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

The purpose of this research study is to see if brain lymphoma treatment that is based on the type of treatment given to people without AIDS can be given safely to people with AIDS who are taking HAART. One of the goals of the study is to see if this therapy results in at least a 2-year remission of the brain lymphoma without the kind of late-occurring brain problems expected with radiation therapy.

Why are you being asked to take part in this study?

You have a disease called AIDS-related primary central nervous system lymphoma. Sometimes this can be referred to as primary brain lymphoma. Lymphoma is a kind of cancer that involves lymphocytes. Lymphocytes are cells that make up part of the immune system. Brain lymphoma is usually a subset of lymphocytes called "B"- lymphocytes. B-lymphocytes in AIDS-related primary brain lymphoma are almost always infected with a virus called Epstein-Barr virus, or EBV. Almost all cases of AIDS-related primary brain lymphoma develop once HIV has caused another kind of lymphocyte called CD4 cells, to become very low. Usually the CD4 cells are less than 50 when the brain lymphoma develops. Before highly active antiretroviral therapy (HAART) was available, the CD4 cells progressively decreased due to uncontrolled HIV infection, and most people eventually had their CD4 cells fall below 50. Before HAART, once the CD4 cells were so low and if brain lymphoma developed, most people survived less than a few months. This is because when the CD4 cells were so low and there was not effective treatment for HIV, other AIDS complications often prevented effective treatment for lymphoma, and people died either of the lymphoma or the other complications of AIDS.

People who do not have AIDS can also develop brain lymphoma. In the past, treatment for brain lymphoma was almost always radiation therapy given to the whole brain. Radiation can make the lymphoma go away. However, many people without AIDS who get radiation to the brain will later develop brain problems due to the radiation they received for the lymphoma. Sometimes these brain problems are so severe that people can no longer take care of themselves, and sometimes these problems can be fatal. As a result, the standard treatments for non-AIDS brain lymphoma have been changing so that radiation therapy is not used as often as it was in the past. Instead, non-AIDS brain lymphoma is generally treated with chemotherapy that is given through a vein, or sometimes taken by mouth. In general, people with brain lymphoma who are treated with chemotherapy live longer with better brain function than was attained with radiation therapy. Chemotherapy in AIDS-related brain lymphoma has not been studied very extensively because people with AIDS-related brain lymphoma tolerate radiation therapy pretty well in the short term, and before HAART was available, they usually died before the late occurring radiation-related brain problems develop. Now that HAART is available, brain lymphoma occurs more rarely, and so it has not been studied well.

Now that HIV can be better managed with HAART, AIDS complications, including non-brain lymphoma, can be treated more effectively. There is some evidence that people with AIDS who develop non-brain lymphoma can be cured of their lymphoma and live for a number of years. There is also some evidence that they can tolerate treatments that are similar to those now used in patients without AIDS. This appears to be due in part to the ability of patients with AIDS to tolerate lymphoma therapy better since HAART was developed, and also because HAART can reduce the other AIDS complications. Therefore, after the lymphoma

therapy has been completed, other AIDS complications can be less of a problem. However, there has not been very much information on the optimal treatment for AIDS-related brain lymphoma since HAART was developed.

How many people will take part in this study?

Up to 28 patients will take part in this research study.

Description of Research Study

This is a research study designed to investigate the use of chemotherapy and HAART in patients with AIDS-related primary brain lymphoma. The study is designed to estimate the percentage of patients treated with the experimental therapy who are alive, free of lymphoma, and who do not have severe brain problems after 2 years from the lymphoma diagnosis.

None of the drugs used in this research study are experimental drugs. Rather, this is research because the drugs are being used in people with AIDS, and for people with AIDS this has not been established as the standard treatment. The treatment consists of highly active antiretroviral therapy selected to be most effective against your HIV infection and easiest for you to take. In addition, there will be six cycles of induction chemotherapy. A cycle lasts for 2 weeks. The chemotherapy consists of high-dose methotrexate and a monoclonal antibody called rituximab (Rituxan®). The combination of high-dose methotrexate and rituximab has not been given in AIDS-related brain lymphoma. It has been given to some patients with non-AIDS-related brain lymphoma in other research studies, but the results of these studies have not been published yet. While the drugs by themselves are tolerated if used appropriately, there is a possibility that in using them together, there would be unpredicted toxicity. High-dose methotrexate is the most commonly used drug in brain lymphoma in people who do not have AIDS. Rituximab is used in certain lymphomas because of its ability to kill B-lymphocytes and lymphoma cells, and it helps other drugs like methotrexate, to kill lymphoma cells. In patients without AIDS who have certain types of lymphomas, rituximab added to chemotherapy results in longer survival and better lymphoma remission compared to chemotherapy given without rituximab. This has not been shown with certainty in brain lymphoma or in any kind of AIDS-related lymphoma. In addition to these drugs, a kind of vitamin called leucovorin will be given. Leucovorin helps to prevent many of the toxic effects of methotrexate. The combination of methotrexate, leucovorin, and rituximab has been chosen based on the possibility that it may be relatively less toxic to your T-lymphocytes compared to most chemotherapy regimens for lymphoma. Most combination chemotherapy regimens for lymphoma can severely deplete T-lymphocytes, including CD4 cells. Part of the research question is to determine the effects of the combination of HAART, methotrexate, leucovorin, and rituximab on your CD4 cells. We want to see if your CD4 cells will increase to a level higher than they were when your AIDS-related brain lymphoma was diagnosed. If the CD4

cells increase, it is possible that better control of AIDS-related complications, and possibly better control of the lymphoma, may occur. It will take 12 weeks to complete the 6 induction cycles of induction treatment. After the completion of induction therapy, if it appears that the lymphoma is completely gone; two additional consolidation cycles of treatment will be given, at 4 week intervals. This treatment will consist only of HAART, high-dose methotrexate, and leucovorin. At the end of these two treatments, only the HAART will be continued.

Some patients may not be able to receive methotrexate, mainly due to problems with their kidneys or heart. In some cases, such patients can also be treated, but their treatment will be modified to include six doses of rituximab over 1 month, combined with HAART, but no methotrexate and no leucovorin.

What will happen if you take part in this research study?

Before you begin the study

One of the other research questions is to determine the level of intellectual function you have after the brain lymphoma has resolved, and to monitor this function over a period of 2 years to see whether there are any long-term effects of the treatment. A series of tests to assess this will be done. Before you start treatment, a short test will be done to determine your ability to understand basic concepts and coordination so that we can know whether the brain lymphoma is causing you severe problems with thinking and concentrating. After the lymphoma appears to have resolved, more formal and intensive tests will be done. The intensive tests will be done each year. Also, shorter interim tests to monitor for any potential problems will be done about every 6 months. In addition, you will have sessions with a specialist who will monitor your understanding of HAART and to help you understand and insure that you are able to take your anti-HIV medications. Some of these tests and sessions may be mentally challenging and for that reason cause you to feel frustrated or embarrassed. If you feel negative feelings about these sessions, please tell your doctors or nurses, or anyone on the health care team. The purpose of these tests and sessions is to help you, and to help us to understand how the treatment affects you, not to embarrass or frustrate you.

To receive the chemotherapy, you will have to be in the hospital at the NIH Clinical Research Center. High-dose methotrexate must be given with intravenous fluid that is mixed with bicarbonate to make the acid in your urine reach a low level. This is to protect your kidneys from the methotrexate. The methotrexate levels in your blood have to be measured every day. The leucovorin has to be given by intravenous injection every 3-6 hours. In rare cases, a drug called glucarpidase (Voraxaze®) may also be used to prevent methotrexate toxicity should you develop problems with your kidneys during treatment. Glucarpidase (Voraxaze®) is given as a onetime dose by intravenous injection.

During the study

Your kidney function, liver function, and blood counts have to be measured by doing blood tests very frequently. It may take 5-10 days to safely stop all of the leucovorin and blood monitoring before you can safely leave the hospital. Therefore, for the first 12 weeks, you will be in the hospital for about a week, every other week. If you have complications or are very sick, you may be in the hospital longer. During the final two consolidation cycles of chemotherapy, you will also spend about 1 week in the hospital getting methotrexate, fluid, and leucovorin. Glucarpidase may be utilized rather than leucovorin or levoleucovorin for methotrexate toxicity in the setting of renal toxicity and delayed methotrexate clearance. The Glucarpidase has to be given by intravenous injection.

You will also be treated with highly active antiretroviral therapy. We refer to this as HAART. There are twenty or more drugs to choose from to treat HIV, but the medications must be taken in appropriate combinations to give the best effect. Your doctors will discuss the specific regimen and alternative regimens with you that would have the best probability of working well for you. HIV grows in the blood, and HAART can inhibit this growth to very low levels. When the HIV is kept at low levels with HAART, the CD4 cells may increase. If the HIV is allowed to grow, the CD4 cells will not increase. They will probably decrease, because HIV kills CD4 cells. The lower the CD4 cells, the more likely you are to get sick with problems related to AIDS. It may be possible to help prevent your brain lymphoma from coming back if the CD4 cells can increase to high levels.

Most anti-HIV medications are taken by mouth. Some are taken by injection. We will discuss the specific drugs with you and provide you with information on the drugs. We will evaluate your understanding of the HAART medications and the need for them periodically in order to help you understand how important they are, and to help us understand any issues involved that make it difficult for you to take all of your medications every day. If you decide you do not want to take HAART, you cannot participate on this research study. If HAART is not able to keep your HIV at low levels, you may not be able to continue participation in the study.

None of the chemotherapy medications or HAART medications in this research study are experimental drugs, because they are all approved by the Food and Drug administration for the treatment of lymphoma or HIV. The experimental part of this study is the combination of HAART and high-dose methotrexate with rituximab and leucovorin in AIDS-related brain lymphoma, because this combination of treatment has not been studied before. Therefore, it is not known whether the treatment will improve your chances to be cured of the lymphoma, or if you will be able to tolerate the treatment. If you are unable to tolerate the treatment, it will have to be stopped.

In order to see the effect of the treatment on your lymphoma, MRI and FDG-PET scans of your brain will have to be periodically repeated. These tests will be done before you start treatment,

and the follow-up tests will be for comparison. The FDG-PET scan will be repeated after the first cycle, again at the time that the MRI suggests all of the lymphoma is gone, and then yearly. The MRI scan will be repeated after the 2nd, 4th, 6th, and 8th treatments, and then every 2 months for 3 times, then every 3 months for 6 times, then every 6 months for 4 times, and then every year for 5 years, or sooner if there is a concern about your brain. If there is evidence that your lymphoma has not completely responded to therapy, you may be offered second-line chemotherapy or whole brain radiation therapy on this protocol.

Because of the relationship of EBV to the brain lymphoma, we want to study what happens to the EBV in your blood and spinal fluid as you get the treatment. Before you start therapy, the EBV will be measured in your blood and spinal fluid. The EBV measurements will be repeated at the time that you appear to have complete resolution of your lymphoma, again at 6 months after completion of treatment, and at any time if it appears the lymphoma may have come back. The spinal fluid will also be examined for any evidence of abnormal cells each time it is examined for the EBV. The repeated analysis of the blood and spinal fluid for EBV is part of the research. Later in this informed consent document, you will find a description of the procedure we use to obtain the spinal fluid. If you agree to allow optional studies (see page 9 of this consent form), additional blood samples (up to 3.5 tablespoons) may be drawn on occasion to store for future studies designed to learn more about cancer, HIV or other diseases. You do not need to agree to optional studies in order to participate in this study.

Periodic eye examinations will be done while you are participating on this study. The reasons for this are that brain lymphoma can sometimes get into the eye. The other reason is that people with low CD4 cells are at risk of certain eye infections.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because of the adverse effects of methotrexate to your baby or unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 3 months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

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

Risks or Discomforts of Participation

This section will discuss a number of issues that you should know about before agreeing to participate in this clinical research trial. In general, the number of tests that are done will be more than if you were treated with standard therapy. You may spend more time at the NIH in the hospital and coming to clinic visits than you would if you were treated with radiation therapy. High-dose methotrexate and rituximab have certain risks associated with their use. The details of these issues follow.

In this research study there are 3-4 repeated evaluations of the spinal fluid for EBV. This requires that spinal fluid be removed from your body. This is done by inserting a small needle between the bones of your vertebral column, which some people refer to as the back bone. The procedure for removing spinal fluid is called a lumbar puncture, and some people call it a spinal tap. Less than 2 tablespoons of fluid are removed. A medicine to numb the skin is first injected in the area where the lumbar puncture is to be performed. After that, a needle is inserted between the vertebral bones into the space where the spinal fluid is. The fluid drains out on its own. After the needle is removed, sometimes the fluid can continue to leak a little bit, and cause headaches. If this happens, we may have to patch the needle hole, but usually it stops on its own. Sometimes if there is a brain lymphoma causing too much pressure in the brain, it is not safe to do a lumbar puncture. One of the reasons to perform the MRI scan is to make sure it is safe to do the lumbar puncture. If it appears that it is not safe, then the lumbar puncture will not be done.

In addition to the lumbar puncture, blood will be drawn from a vein. The amount of blood varies depending on what other tests are being done. For the purpose of looking for EBV in the blood, about 1 teaspoon of blood will be drawn. Additional blood tests, including to check your HIV viral load and CD4 cell counts and routine blood work to check for any toxicity related to the treatment can required up to 14 tablespoons (but usually much less) of blood to be drawn. This amount of blood is not dangerous to draw from you.

MRI scans can make some people feel claustrophobic. The MRI machine is noisy, and you have to lie very still while the machine scans your brain to take a picture of your lymphoma. If you have feelings of claustrophobia, it is important to tell us so that we can help you with this.

The FDG-PET scans require that you not eat for 12 hours before the scan. You have to lie very still in the FDG-PET scan machine while the scan is being done. Before you get the scan, a radioactive medication with sugar (the FDG) will be given you by vein. The FDG accumulates in the lymphoma more than it does in the normal brain, and it is a sensitive way to visualize the brain lymphoma. The test requires you lie very still for up to an hour while the scan is being done.

We will now discuss the treatment medications and toxicities:

HAART

It is a requirement that you take HAART on this research study. HAART probably should be taken every day for your entire life, unless at some future point an improved kind of therapy for HIV is developed or you decide you no longer want to be treated for your AIDS. HAART can have side effects. Some of the side effects can come very quickly. The specific side effects depend on the specific medications that make up your HAART regimen. These side effects can include headaches, nausea, diarrhea, fatigue, trouble sleeping, bad dreams, anemia, liver function problems, and pancreas problems. Usually we can change the medications to minimize these kinds of side effects, and most people are able to take HAART without having many side effects. HAART can also have longer-term side effects. These longer-term side effects can include changes in fat metabolism and the distribution of fat on your body. Certain drugs seem to be more likely to cause these kinds of side effects, and we will avoid them whenever possible. In general, we will try to devise a regimen that has the least likelihood of causing you either short-term or long-term side effects, and use the fewest number of pills possible. However, sometimes this is not possible, and the only way to keep the HIV from growing is with drugs that have some side effects, and sometimes requires more medications. The specific toxicities of each medication you take will be discussed with you.

If you currently have an infection that is very mild or without symptoms, HAART could temporarily worsen your clinical condition by making your body react more to it—this is called Immune Reconstitution Inflammatory Syndrome or IRIS. It is also possible that IRIS can occur in your brain as your immune system recovers and reacts to your primary central nervous system lymphoma. This may lead to a temporary worsening of neurologic symptoms. If you have IRIS to another infection or your lymphoma, you will get treatment for the infection or continued lymphoma therapy, and will also receive steroids to treat the IRIS reaction.

Rituximab

Rituximab is a monoclonal antibody, meaning it reacts with a specific protein. The protein it reacts to is called CD20, which is found on some B-lymphocytes, including most B-cell lymphomas. The drug is given by intravenous injection. During infusion, it can sometimes cause a reaction of blood pressure changes, chest tightness with difficulty breathing, back pain, shaking chills, and a severe allergic reaction, which can rarely be fatal. Rituximab can cause low blood counts, muscle aches, joint pains, nausea, vomiting, diarrhea, and itching. You may be given acetaminophen and diphenhydramine to help prevent reactions related to rituximab.

Rituximab appears to be more toxic to some people with AIDS compared to people without AIDS. In a randomized study of non-brain lymphoma in people with AIDS, some people were given rituximab and combination anti-lymphoma chemotherapy with HAART, and others were given only the combination chemotherapy and HAART, but no rituximab. More people in the

group that received rituximab had infections, and more people in the group that received rituximab died from complications related to the treatment. Most of the people who died of treatment-related complications had low CD4 cells. In order to minimize infectious complications while taking part in this study, you will receive medications to prevent infection. You will be monitored closely for infections both while you are receiving therapy, and during the time period after therapy in which your immune system is recovering.

In this study, most people who will be treated with rituximab also will have low CD4 cells. It is not known whether the treatment with methotrexate and rituximab will have the same potential for causing problems as the combination anti-lymphoma chemotherapy and rituximab did in the randomized trial.

High-dose methotrexate with leucovorin rescue

The doses of methotrexate given in this research are very high. Many of the toxicities of high-dose methotrexate can be prevented or reversed with leucovorin, a vitamin. We call it leucovorin rescue because the doses of methotrexate given are too high to be given safely without the leucovorin.

High-dose methotrexate can cause nausea, vomiting, and sores in the mouth, throat, stomach, intestines, and anus. It can cause the bone marrow to stop making blood cells, and this can lead to infections, anemia (low red blood cells), and bleeding. Methotrexate can cause you to lose all of your hair, but when leucovorin is administered, hair loss may be decreased.

The methotrexate can cause your kidneys to stop functioning. Your kidney function will be assessed prior to each dose of methotrexate, and it will not be given if there is evidence of poor kidney function that would make it too dangerous for you to get methotrexate. To help prevent kidney problems, you will receive large amounts of fluid by vein before the methotrexate is given. The fluid will contain bicarbonate so that we can adjust the acid content of the urine. Reducing the acid content in the urine protects the kidneys. The fluid will have to be continued for several days. Sometimes the kidneys can be damaged even when the precautions are taken. If this occurs, higher more frequent doses of the leucovorin are given to try to reverse this and to prevent additional toxicity. If the kidney failure is severe enough, dialysis may be necessary to help support you. Kidney failure due to methotrexate can become life threatening, although this is not common when hydration and leucovorin are used to prevent it. In addition, a new drug called glucarpidase (Voraxaze®) has been used to decrease the methotrexate levels. Glucarpidase (Voraxaze®) is not yet approved by the FDA, but the Cancer Treatment Evaluation Program at the National Cancer Institute can supply the drug if your condition appears such that you would benefit from it. If you need the glucarpidase (Voraxaze®), the drug will be explained to you in detail, and a separate informed consent will be provided to you for review before you consent to be treated with it.

You should not be pregnant or plan on becoming pregnant while being treated with methotrexate. Your sperm should not be used to impregnate while you are receiving a treatment regimen that includes methotrexate.

Many medications can decrease the ability of the kidneys to excrete methotrexate, and so you should not be on Bactrim, penicillin, aspirin, or nonsteroidal anti-inflammatory drugs such as ibuprofen while getting methotrexate.

Leucovorin (or levoleucovorin) is usually well tolerated, but can sometimes cause an allergic reaction. Most often it will be given by intravenous infusion, but if when your methotrexate levels are low enough and if you are able to drink lots of fluids and take oral medication, the leucovorin (or levoleucovorin) may be given by pill form.

Filgrastim

Filgrastim in a medication that is injected which can help to keep your white blood cells from being too low for long periods of time. If your white blood count goes too low, you will be treated with filgrastim injections. These can cause local irritation at the injection site, bone and muscle pain, and sometimes fevers.

Glucarpidase

Glucarpidase usually well tolerated, but can sometimes cause an allergic reaction. The most common adverse reactions (incidence >1%) with glucarpidase include paraesthesias, flushing, nausea and/or vomit, hypotension, and headache

Potential Benefits of Participation

Methotrexate is a standard treatment for primary brain lymphoma, and there is a reasonably good chance that the treatment will have beneficial treatment effect on your lymphoma. It is important to realize that if the treatment is not effective, you may not receive any benefit from participation. If the treatment does not work, and if it appears that you would need to have radiation therapy to your brain, it is theoretically possible that the toxicity effects of radiation might be worse because you have already received methotrexate. If other medical or chemotherapy-based treatment options are reasonable, we will recommend that as an option to radiation. However, if the rituximab and methotrexate work and the lymphoma does not come back, and you do not have to receive radiation therapy, you are not at risk for developing radiation-related brain problems. Additionally, HAART and its effects on your HIV will be monitored carefully while you are on the research study.

Increasingly, rituximab has become a standard treatment for primary brain lymphoma in patients without AIDS, including those who have other forms of immune system suppression, for example, due to medications used in organ transplant. For patients who cannot receive high dose methotrexate due to other health problems, it is possible that HAART and rituximab alone may effectively treat your brain lymphoma and spare the need for radiation. During your treatment, you will be monitored closely, and if this treatment does not work, additional chemotherapy or radiation therapy will be offered to you.

Alternative Approaches or Treatments

The most common treatment that is given for AIDS-related brain lymphoma is radiation therapy to the whole brain. The lymphoma goes completely away in almost everyone with AIDS-related brain lymphoma who receives whole brain radiation. Before the HAART was available, many people with AIDS-related brain lymphoma would have a recurrence of the lymphoma after the radiation was given. After the whole brain is radiated, additional radiation may not be possible because it can cause too much damage to the normal brain. Now that HAART is available, it is possible that the lymphoma may be less likely to come back after whole brain radiation, particularly if the CD4 cells increase with HAART. However, many people with brain lymphoma not related to AIDS develop problems with their brain after being treated with radiation and it may be that the risk of these problems occurring after radiation in AIDS-related brain lymphoma could be a problem. How often this occurs in AIDS patients is not known. It is known that patients with HIV infection have greater radiation-related toxicity to certain tissues, such as the gastrointestinal tract and mucous membranes. This does not mean that people with HIV will absolutely be at greater risk than HIV-negative people for brain problems after radiation for brain lymphoma. Because there is not sufficient information to know what the risk of brain injury is from radiation, and because it is considered the standard treatment for AIDS-related brain lymphoma, it is a reasonable option to consider instead of being treated on this experimental study.

There are other chemotherapy approaches that may be reasonable to consider for AIDS-related brain lymphoma. The chemotherapy given in this research study does not contain as many anti-lymphoma drugs as the chemotherapy regimens for non-AIDS brain lymphoma. That raises the question of whether the chemotherapy in this study will work as well as the regimens for non-AIDS brain lymphoma. The answer to that question is not known, and this research study may help to answer that question. It may be reasonable to consider having the same treatment as is given to people without HIV. The treatments given to people without HIV tend to destroy the CD4 cells however, and this could potentially be a problem with AIDS-related brain lymphoma.

A few people have taken only HAART for their AIDS-related brain lymphoma. Very rarely this may work, and the lymphoma can go away just by taking HAART. This has only been

rarely reported in the medical literature. This is a reasonable option if you do not want to receive aggressive therapy for your lymphoma and would rather die of your lymphoma than to fight it very hard, but want to do something that may have a small chance of making things better. This is reasonable for people who feel that the prognosis for AIDS-brain lymphoma is so bad that they do not want to spend time in the hospital getting treatment that cannot guarantee them a high probability of cure. There is not treatment available for AIDS-brain lymphoma that can guarantee a high probability of cure with years of good life after the treatment is finished, but this research study is an attempt to begin working toward that goal. Because of this however, some people may feel that they would rather not even take HAART, and that they would just like to be made comfortable and not suffer. For some people this is a reasonable option.

Research Subject's Rights

What are the costs of taking part in this study?

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.

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 National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board

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.

Stopping Therapy

Your doctor may decide to stop your therapy 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 your doctor thinks are too severe
- if new information shows that another treatment would be better for you

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 to 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 can**not** be recalled and destroyed.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

You should also know that there are several circumstances in which the Certificate does not provide coverage. These include when information:

- will be used for auditing or program evaluation internally by the NIH; or

- must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA).
- is necessary for your medical treatment and you have consented to this disclosure;
- is for other research.

In addition, identifiable, sensitive information protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

Conflict of Interest

The National Institutes of Health 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 additional information or 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.

One or more investigators participating in this study may have less than $15,000 of stock in the manufacturer of the product(s) used in this study. Under federal regulations, however, this is permissible and does not create 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 and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. If you have given permission for your samples to be used for research on

another protocol, they may be used as described in that protocol. Otherwise, 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/or 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.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The 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 National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. 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. Robert Yarchoan**, M.D., Building 10, Room **6N106, Bethesda, MD 20892**, Telephone: 240-760-6075. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director at 240-760-6070.

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

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JUNE 26, 2017 THROUGH JUNE 25, 2018.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____