

MEDICAL RECORD

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

• Adult Patient or • Parent, for Minor Patient

INSTITUTE: NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

STUDY NUMBER 91-DK-A1-213 PRINCIPAL INVESTIGATOR: Jay H. Hoofnagle, M.D.

STUDY TITLE: A Four-Week Course of FIAU for Chronic Hepatitis B

INTRODUCTION

We invite you (or your child) to take part in a research study at the National Institutes of Health. It is important that you read and understand several general principles that apply to all who take part in our studies: (a) taking part in the study is entirely voluntary; (b) personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others; (c) you may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled. The nature of the study, the risks, inconveniences, discomforts, and other pertinent information about the study are discussed below. You are urged to discuss any questions you have about this study with the staff members who explain it to you.

As a patient with chronic hepatitis B, you are invited to take part in this research study designed to test the medication FIAU for its effect on your liver disease. The full name of FIAU is 1-2' deoxy-2' fluoro-1-beta-D-arabinofuranosyl-5-iodo-uracil. This medication was developed originally to treat herpesvirus infections and is similar to other antiviral drugs such as AZT and acyclovir. FIAU has recently demonstrated activity against hepatitis B. We used FIAU to treat six patients who had AIDS and hepatitis B. We found that FIAU led to a rapid decrease in levels of hepatitis B virus in the blood, and in some patients this decrease lasted for weeks to months. An effect on hepatitis B virus lasting this long may be permanent. In further studies, a much lower dose of FIAU was found to inhibit hepatitis B just as well as the higher dose. In these studies, patients were treated for only 14 days, which may not be long enough to cure hepatitis B virus infection. On the other hand, longer treatment may lead to more side effects. For these reasons, this study will test four different doses of FIAU given for 28 days.

Therefore, we are asking you to enter this study in which you will receive FIAU for 28 days. At the beginning you will be assigned to receive one of four doses of FIAU, which are equivalent to the doses of FIAU used in the original studies. Both during and after treatment you will be monitored closely for any side effects or changes in your chronic hepatitis. You will be told about any significant findings from this study (whether positive or negative) regarding the effects of FIAU on chronic hepatitis, and you will be informed if any alternative treatments become available during the course of this study.

PATIENT IDENTIFICATION

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

• Adult Patient or • Parent, for Minor Patient

MEDICAL RECORD

CONTINUATION SHEET for either:
NIH 2514-1, Consent to Participate in A Clinical Research Study
NIH 2514-2, Minor Patient's Assent to Participate in A Clinical Research Study

STUDY NUMBER: 91-DK-AI-213 CONTINUATION: page 2 of 6 pages.

This is an experimental study. It has not yet been proven that FIAU is effective in treating hepatitis B, and its side effects have not been studied in many patients. At the present time, however, treatment for hepatitis B is not very satisfactory. Alpha interferon has been effective in some patients with hepatitis B. For instance, we find that 40% of patients respond to interferon treatment with long-term improvement in their liver condition. The remaining 60% of patients, however, do not obtain lasting benefit. Because interferon has to be given by injection, has frequent side effects, and only benefits fewer than half of patients, we continue to search for better treatments for hepatitis B.

Interferon, however, does work in some people. If you have never been treated with interferon, it may be best for you to try interferon before you enter this study. In general, we find that persons with severe hepatitis B have a high likelihood (greater than 50%) of responding to interferon, whereas persons with relatively mild disease are unlikely (less than 10%) to respond. Therefore, if you have a severe case of hepatitis B, you should try treatment with interferon first. If you have a mild or moderate case, trying FIAU before interferon is reasonable. However, if you do not have long-lasting improvement after treatment with FIAU, you should at some time in the future receive a course of interferon. Of course, if you have received interferon in the past and have not responded or couldn't tolerate its side effects, a reasonable decision on your part would be to enter this study of FIAU.

NATURE OF STUDY

This study will last approximately six months. At the start you will be admitted to the National Institutes of Health (NIH) Clinical Center for a complete medical examination and liver biopsy. You will then begin taking FIAU. You will be watched closely to monitor the effect of FIAU on your hepatitis and for any side effects. A complete explanation of this study is given below:

- (1) You will be admitted to the Clinical Center where we will do a complete medical history and physical examination.
- (2) You will have a series of laboratory studies to define your overall medical condition, the degree of liver disease, and level of hepatitis virus infection. These studies will include multiple blood tests, a urine analysis, and a 24-hour urine collection, a chest X-ray and electrocardiogram (heart tracing), and a abdominal ultrasound (sound-wave test to evaluate the liver). If you are a woman, you will have a pregnancy test. One blood test that you will have is for antibody to the human immunodeficiency virus (anti-HIV), the cause of acquired immune deficiency syndrome (AIDS). You will be notified promptly of the results of the anti-HIV test.

PATIENT IDENTIFICATION

CONTINUATION SHEET for either:

NIH-2514-1 (10-84)

MEDICAL RECORD

CONTINUATION SHEET for either:
NIH 2514-1, Consent to Participate in A Clinical Research Study
NIH 2514-2, Minor Patient's Assent to Participate in A Clinical Research Study

STUDY NUMBER: 91-DK-AI-213 CONTINUATION: page 3 of 6 pages.

If you are found to have this antibody (anti-HIV), you will be expected to inform your sexual partner(s) that they may have been exposed to this virus. We will help you and your sexual partner(s) obtain information regarding the meaning of this test and ways of preventing spread of this infection. This test will be repeated at the end of the study.

(3) At the beginning of this study, you will undergo a liver biopsy to assess the degree of injury done to the liver by your chronic hepatitis. You will not have to have a liver biopsy if you have had one within the last year. This procedure will be fully described to you and you will be asked to sign a separate consent form for this liver biopsy.

(4) You will then be assigned to a dose of FIAU and will begin taking it. Four doses of FIAU are being evaluated; the dose that you receive will be based upon the order in which you enter the study. FIAU is given in the form of a liquid suspension that you will drink three times a day for 28 days. You will be taught in the clinic how to measure out the correct amount of FIAU so you can take it at home.

(5) While taking FIAU you will be seen on day 3 and then weekly in the clinic and have blood drawn to carefully monitor side effects and the effects of FIAU on the hepatitis. On one day during the first week and on one day during the last week of treatment you will be asked to stay in the outpatient clinic for a few hours to have your blood drawn immediately before you take the FIAU and exactly 2 hours afterwards. This is to measure how well you absorb FIAU and whether its levels slowly build up during treatment.

(6) After treatment you will be seen in the clinic for brief visits and to have blood drawn every one to two months until six months after starting FIAU when you will have a thorough evaluation in the outpatient clinic which will include a medical history, a physical examination, multiple blood tests and a urine test. At that point, this study will be over, but you will be eligible to enter other studies of therapy for chronic hepatitis B or to be followed without treatment in the outpatient clinic.

(7) If you are capable of bearing or fathering children, you will have to practice an effective method of birth control (both men and women) for the 28 days of treatment and for two months thereafter. The risks of FIAU to an unborn fetus or to developing sperm are not known. If you are pregnant you cannot participate in this study.

PATIENT IDENTIFICATION

CONTINUATION SHEET for either:

NIH-2514-1 (10-84)

MEDICAL RECORD	CONTINUATION SHEET for either: NIH 2514-1, Consent to Participate In A Clinical Research Study NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study
----------------	---

STUDY NUMBER: 91-DK-A1-213 CONTINUATION: page 4 of 6 pages.

RISKS AND DISCOMFORTS

(1) The local pain or discomfort of having blood drawn. You may have as many as 20 blood drawings during the six months of this study. No more than 14 ounces (approximately 28 tablespoonfuls) of blood will be taken for research purposes during any six-week period. Drawing blood occasionally causes a bruise in the skin where the needlestick occurs. Rarely, fainting occurs after blood drawing.

(2) The pain and risks of liver biopsy. Liver biopsy is performed using a needle that is passed through the skin into the liver to obtain a piece of liver about two inches long and 1/16 of an inch in diameter. About 20% of persons having a liver biopsy have some degree of pain over the liver that may last from a few minutes to several hours. This rarely requires pain medication and always disappears within a day or two. Some patients faint after liver biopsy. This can usually be avoided and can be treated if it occurs.

Some rare complications of liver biopsy are infection, puncture of another internal organ, and bleeding. Infections in the blood can occur after a liver biopsy but they can be treated with antibiotics. Puncture of another internal organ such as the lung, gall bladder, intestine, or kidney can occur when a liver biopsy is attempted. To prevent this, we always perform an ultrasound before the biopsy to identify where all the internal organs are and where it is best to carry out the liver biopsy. A rare complication of liver biopsy is severe bleeding such that a blood transfusion or even an operation to sew up the hole in the liver is needed. This complication which occurs less than one in 1,000 times. In less than one in 10,000 cases, death has occurred from bleeding after a liver biopsy. At the time of the liver biopsy you will be given a more complete and detailed consent form that outlines how the liver biopsy is done and its complications.

(3) The risks and discomforts of taking FIAU for 28 days. FIAU is a new medication, and its side effects have not been completely described. In studies of persons taking FIAU for 14 days, it was very well tolerated. Some side effects that have been reported or could occur are:

- (a) Fatigue, irritability, trouble sleeping (insomnia). These are mild and disappear when treatment is stopped.
- (b) Nausea and upset stomach. These intestinal complaints are common with the highest dose of FIAU that we will be using. These side effects are usually mild and disappear quickly when treatment is stopped.
- (c) Skin rashes. Rarely patients who take drugs similar to FIAU develop mild, red, itchy rashes that last a few days only.

PATIENT IDENTIFICATION	CONTINUATION SHEET for either: NIH-2514-1 (10-84) NIH-2514-2 (10-84)
------------------------	--

MEDICAL RECORD

CONTINUATION SHEET for either:

NIH 2514-1, Consent to Participate in A Clinical Research Study

NIH 2514-2, Minor Patient's Assent to Participate in A Clinical Research Study

STUDY NUMBER: 91-DK-AI-213

CONTINUATION: page 5 of 6 pages.

(d) Bone marrow suppression, or a decrease in the red and white blood cells and platelets in the blood. Drugs similar to FIAU may lower the number of red blood cells, making some patients mildly anemic, or lower the number of white blood cells, which make up your immune system, thereby making you more susceptible to infections. However, you are unlikely to develop a serious infection because we will stop treatment if the white blood cell count falls too low. Drugs like FIAU can also decrease the number of platelets, which are responsible for blood clotting. A low platelet count may make you more prone to bleeding, but this should not cause serious bleeding. The effects of FIAU on the bone marrow will be monitored closely, and the dose will be lowered if the white blood cell or platelet count decrease too much. All of the bone marrow side effects have been mild in the few patients who have been treated with FIAU and they resolved quickly when treatment was stopped.

(e) Seizures. Some patients receiving very high doses of drugs similar to FIAU have developed seizures. These patients had AIDS and many serious problems, and the doses used were much higher than you will receive. Also it is still not clear whether the seizures were due to the treatment or to the underlying AIDS in these very ill patients.

(f) Pains in the arms and legs can occur with high doses of FIAU. This side effect is also seen with other antiviral medications and may be due to irritation of the nerves or the muscles of the arms and legs. These pains can be severe and last for weeks to months. In some cases, a permanent decrease in nerve function is found. Because of this side effect, we are testing low doses of FIAU and are monitoring patients carefully. If you develop leg or arm pains, we will stop the FIAU and treat you with pain medications.

If you develop a severe side effect such as nerve and muscle pains, seizures, large decreases in the blood cell counts, or extreme fatigue, we will stop the FIAU. In addition, if you are a woman and become pregnant, FIAU will be stopped.

BENEFITS

The benefits of participating in this study are the following:

- (a) You will have a thorough medical evaluation of your condition.
- (b) Your chronic hepatitis B may improve as a result of treatment.

PATIENT IDENTIFICATION

CONTINUATION SHEET for either:

NIH-2514-1 (10-84)

MEDICAL RECORD	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient	continuation: page <u>6</u> of <u>6</u> pa
----------------	--	---

91-DK-AI-213

STUDY NUMBER: _____

OTHER PERTINENT INFORMATION

- Confidentiality.** When results of a study such as this are reported in medical journals or at meetings, the identification of those taking part is withheld. Medical records of Clinical Center patients are maintained according to current legal requirements, and are made available for review, as required by the Food and Drug Administration or other authorized users, only under the guidelines established by the Federal Privacy Act.
- Policy Regarding Research-Related Injuries.** The Clinical Center will provide short-term medical care for any physical injury resulting from your participation in research here. Neither the Clinical Center nor the Federal government will provide long-term medical care or financial compensation for such injuries, except as may be provided through whatever remedies are normally available under law.
- Payments.** If you are a patient, you are not paid for taking part in NIH studies. Exceptions for volunteers will be guided by Clinical Center policies.
- Problems or Questions.** Should any problem or question arise with regard to this study, with regard to your rights as a participant in clinical research, or with regard to any research-related injury, you should contact the principal investigator, Dr. Jay H. Hoofnagle, or these other staff members also involved in this study: Dr. Stephen Straus, Dr. Adrian Di Bisceglie ; _____ :
 Building 10, Room 4-D-52, Telephone: (301) 496-1721
 National Institutes of Health
 Bethesda, Maryland 20205
- Consent Document.** It is suggested that you retain a copy of this document for your later reference and personal records.

COMPLETE APPROPRIATE ITEM BELOW, A or B:

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 & Date Signed

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) & Date Signed

 (if other than parent, specify relationship)

 Signature of Investigator & Date Signed

 Signature of Witness & Date Signed

PATIENT IDENTIFICATION

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

• Adult Patient or • Parent, for Minor Patient

MEDICAL RECORD**INFORMED CONSENT STATEMENT FOR HIV BLOOD TESTING**

We request your permission to test your blood for the presence of antibodies to the Human Immunodeficiency Virus (HIV), the virus that causes Acquired Immune Deficiency Syndrome (AIDS). In order to perform the test, a small amount of blood (approximately 2 teaspoons) will be withdrawn from one of your arms with a needle. You may experience some slight discomfort at the needle entry site and there may be some bruising. In addition, there is a very small risk of your fainting or of infection at the needle entry site. If your test results are found to be positive, or if you are otherwise diagnosed as having AIDS, you should be aware of the following Clinical Center HIV Testing Policy:

1. Your physician will notify you promptly of the HIV test results.
2. Your physician and/or the Clinical Center HIV counselor will offer you, and any current and/or ongoing sexual partner(s) (spouses are generally considered to be current or ongoing sexual partners) or needle-sharing partner(s) you identify, information on the meaning of the test results and how to prevent the spread of the infection.
3. Because the virus may be transmitted in several ways, it is important that you inform sexual and/or needle-sharing partner(s) that any, or all, of them may have been exposed to the HIV virus and encourage them to be tested. If you request it, staff at the Clinical Center will assist you in notifying your partner(s) and arrange counseling for them through an HIV counselor.
4. The results of your HIV test and/or documentation of the diagnosis of AIDS will become a part of your Clinical Center medical record and, as such, will be protected from unauthorized disclosure by the Federal Privacy Act of 1974. In general, access to your medical record will be restricted to those health care professionals directly involved in your care or in the conduct of ongoing biomedical research, and information is not usually released to other third parties without your permission or that of your designated representative. However, there are some particular routine uses of such information of which you should be aware.
 - a. If you are unwilling or unable to notify your partner(s), the Clinical Center is responsible for attempting to contact and inform them of their possible exposure to the virus. Reasonable attempts will be made to protect your identity including withholding your name when notifying any partner(s) of their possible exposure. Some notification or counseling of current and/or ongoing partners may be carried out through arrangements with, or referral to, local public health agencies.
 - b. A summary of your care at the Clinical Center will be sent to the physician who referred you here for treatment.
 - c. The Clinical Center may report certain communicable diseases, including AIDS, to appropriate State and Federal government agencies.

If you have any questions regarding the HIV testing or the information provided above, you are encouraged to discuss them with your physician and/or a Clinical Center HIV counselor (496-8955).

Complete Appropriate Item Below, A or B:

A. Adult Patient's Consent: I have read the explanation about the blood testing and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this blood testing.

Signature of Adult Patient

Date

Signature of Witness

Date

Patient Identification

B. Parent's Permission for Minor Patient: I have read the explanation about the blood testing 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 blood testing.

Signature of Parent(s)

Date

(If Other than Parent, Specify Relationship)

Signature of Witness

Date

**INFORMED CONSENT STATEMENT FOR
HIV BLOOD TESTING**
NIH-2663 (2-89)