INSTITUTE: National Institute of Allergy and Infectious Diseases (NIAID)

STUDY NUMBER: 13-I-0062 PRINCIPAL INVESTIGATOR: Dr. Frank Maldarelli

STUDY TITLE: A Double Blind Randomized Placebo Controlled Study Examining the Effects of a Non-absorbable (Rifaximin) Antibiotic on the Chronic Immune Activation Observed in HIV-infected Subjects

Continuing Review Approved by the IRB on 05/23/16
Amendment Approved by the IRB on 07/20/15 (I) Date Posted to Web: 06/01/16
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.

DESCRIPTION/PURPOSE OF RESEARCH:

You are being invited to participate in this research study because you are HIV-infected and are taking medications (antiretroviral therapy [ART]) for treating this infection. HIV treatment can control HIV, but therapy does not provide a cure. The reasons why therapy does not cure HIV infection are not well understood. HIV persists in blood cells for years, even while people are taking ART. In addition, HIV infection leads to an activated immune system, which can contribute to persistence. Immune activation improves, but does not fully resolve with ART. A better understanding of HIV and the immune activation HIV causes will help understand HIV persistence and identify new strategies to eliminate HIV infection.

In this study, we are investigating the source of immune activation in HIV infection. In general, chronic immune activation may be thought of as an exaggerated response to infection. It is not clear why HIV-infected patients have this exaggerated response. One theory why HIV infection causes immune activation has to do with the gastrointestinal tract. HIV infects immune cells the intestine (gut) soon after infection and causes damage to the intestinal immune barrier. The damage to the intestine lets bacterial products cross into the blood stream, leading to ongoing inflammation. Even when a person with HIV feels well, this chronic leakage of bacterial products may affect the immune system.
In this study, we are planning to investigate whether taking Rifaximin, an antibiotic used to reduce bacteria in the intestine, will reduce leaking of bacterial products into the blood stream. Rifaximin is taken by mouth and is designed to stay inside the digestive system, so its effects on bacteria are only within the intestines.

Rifaximin is approved by the Food and Drug Administration (FDA) for treating people with traveler's diarrhea with a particular bacteria (called "noninvasive E. coli") and to reduce the risk of liver related encephalopathy that arises from increased gut bacteria. Individuals with traveler's diarrhea usually take Rifaxixmin for several weeks. Individuals at risk for hepatic encephalopathy take Rifaximin for many months at a time. In this study we are using Rifaximin to reduce bacteria in the gastrointestinal tract, which is a research purpose, and not for an FDA indicated purpose; this is considered an "off-label" use of Rifaximin. Participants in the study will take 550 mg of Rifaximin twice a day, which is a dose approved by the FDA. Participants in the study will be taking the active drug, Rifaximin, for part of the time, and a placebo (sugar pill) part of the time; this is a blinded study and you will not be told which medication (Rifaximin or placebo) you are taking. The study drug and the placebo will be provided free of charge to participants.

This study will take place at 3 different sites: The Walter Reed National Military Medical Center [WRNMMC], the University of Pittsburgh and the National Institute of Health [NIH]. You will be part of this study for a maximum of 20 weeks. The study duration may be extended if you need to receive other therapy, such as antibiotics or a vaccine, during the course of the study. A total of 44 subjects are expected to take part in the study. As many as 20 subjects may be enrolled at the NIH Clinical Center however we may check as many as 200 patients to see if they qualify to be in the study.

You will be asked to come to the clinic for up to 13 visits; some visits are required and some are optional. The visits include 2 screening visits to make sure that you are qualified to be in the study. It may be necessary for you to return every week to the clinic. Each visit will last approximately 2 hours, but the screening visits when you first come to the clinic may take longer.

PROCEDURES:

During the screening visits, we will do routine blood tests to see if you qualify for the study. If you do not qualify for the study, your participation will end at this time. If you do qualify for the study, and you choose to be in the study, you will be randomly assigned (by chance, like the flip of a coin) to start taking either the antibiotic, Rifaximin, or the placebo (a 'sugar pill' that should have no effect on you).

You will take one of the two study medications (Rifaximin or the placebo) for 4 weeks, then stop for 4-6 weeks, then you will be given the other study medication for 4 more weeks. Then you will stop all study-related products and return to the outpatient clinic for a follow-up visit after an additional 4 weeks.

While in this study, if you need to take an antibiotic, or steroids, or change other medications for any reason, you must tell your study team right away. If you need to take an antibiotic or stop your other medications, your study participation may need to be temporarily or permanently stopped. You may be able to restart the study in some cases. Additionally,

while taking part in this study you will be unable to take some supplements that are referred to as "probiotics". The details of these restrictions will be explained to you in detail, to make sure you understand.

While on this research study you will have visits that will include a review of your symptoms, and blood and urine tests; you will be asked to provide a stool sample on several occasions, which will be used in specialized tests, and have a physical exam if needed. The blood and urine will be used in both standard and specialized tests.

The standard tests will include:

- Tests to determine the health of your liver, kidneys, as well as your blood cell counts
- Your pregnancy status (if applicable) will be tested with a urine test

If your blood and urine tests show that you can be in the study, and you choose to be in the study, then you will also have some specialized tests on your blood and stools.

The specialized tests include tests to:

- Determine the HIV viral load (a measure of the amount of virus in your blood)
- Study the effects of Rifaximin on your immune cell functions
- Study the effects of Rifaximin on markers of inflammation
- Study the effect of Rifaximin on the level of the passage of bacterial products across the lining of your intestines
- Study the effect of Rifaximin on the bacterial flora (normal bacteria found in the intestines) in stool samples

There are 11 required study visits in this study; two screening visits occur within 70 days of starting the study, which will determine whether you are eligible to participate. If you are eligible and decide to participate, study visits will occur on day 0 (when you will start the either Rifaximin or placebo), 7, 14, and 28 (when you complete the first phase and start the washout phase), 57 (when you start either the placebo or the Rifaximin), 64, 71, and 85 (when you stop the Rifaximin or placebo), and 113; there is some flexibility for some of the visits. Each of the visits will take approximately 2 hours to complete. You may be asked to have additional testing, if needed, while on the study.
The washout phase is 4 weeks in duration. Vaccines, such as a flu vaccine, and some medications, like antibiotics or steroids, might affect the results of the study. If you require vaccines or such medications during the washout period, we will extend the duration of the washout period. If you require a vaccine during the washout phase, we will extend the washout to a total of six weeks. If you require antibiotics or steroids during the washout phase, we will extend the washout phase by 4 weeks from the time you stop the antibiotics or steroids. Several of the blood samples time points are absolutely necessary for the trial analysis. Very infrequently (less than 1 percent of the time) samples may have issues in transport or processing and you may have already started the medication for the phase. In the very unlikely possibility that such a situation exists with an essential time point, we will perform a four week washout and restart the phase.

a- In both study phases 1 and 2, an additional optional blood draw may occur on Day 3 of study phases 1 and 2
b- physical exams will be performed as needed
c- Colonoscopy procedures are optional.

For this study, there will be a maximum of 11 required blood draws. The total amount of blood drawn will be about 800 mL (about 27 ounces, about three and a half cups). For comparison, the standard blood donation is about 450 mL (2 cups). We will not draw more than 550 mL of blood over any 8 week period.

Optional Procedures
There are 2 additional procedures that will help us see how Rifaximin may affect people with HIV infection.

1. Two additional blood draws, which will involve additional clinic visits: One on the third day after you start Rifaximin, and one on the third day after you start placebo.

2. Colonoscopies of your lower intestine, and biopsies of your intestine. These studies will provide samples of your gastrointestinal tract, and are important to help us understand the effects of Rifaximin in the study. You have the option of participating in up to three colonoscopies. If you elect to have one colonoscopy, it will be done at approximately the end of the second treatment phase of the study (approximately day 85 from the day the study starts). If you choose two colonoscopies, they will be done at days 28 and 85 from the day the study starts. If you choose to have three colonoscopies, one will be done prior to the start of the study, and at approximately days 28 and 85. Colonoscopy is explained in detail below. These procedures are optional and you do not need to have them in order to be in this study. If you agree to have the colonoscopies, an experienced gastroenterologist will perform the colonoscopy and obtain up to 60 biopsies (samples of the intestinal tissue). We will perform the colonoscopy as part of a separate protocol with a separate consent. We will discuss those details should you decide to have the colonoscopy. You will receive the results of your colonoscopy, and the findings will be discussed with you.

RISKS OR DISCOMFORTS:

The possible risks and discomforts from being in this research study include risks from the study medication, blood draws, and the possible loss of privacy. In addition, if you choose to have the colonoscopy procedures, there are additional risks associated with the procedure and the anesthesia that is given during the procedure.

MEDICATION

Rifaximin- is generally well-tolerated. In a small number of cases (about 2%) of those who took Rifaximin in earlier studies reported side-effects such as gas, headache, abdominal pain, pain in the rectum when you have a bowel movement, an urgent need to have a bowel movement, nausea, constipation, vomiting, and fever. Rifaximin changes the kinds of 'normal' bacteria in the intestine, and may cause some intestinal bacteria to become resistant to antibiotics, but this is not expected to cause a problem during the study, and is expected to resolve soon after you stop the medication. Please contact your case manager if you begin to experience side effects during the course of the study. It is very important to continue your antiretroviral medications, and we will review all of your medications during study visits and in the event you are experiencing side effects.

As with many drugs, some people may be allergic to the medication. This may result in itching, a rash, hives, and less commonly, exfoliative dermatitis (a severe rash where the skin might slough off), and swelling of the throat. In addition, the use of any antibiotic (including Rifaximin) may be associated with an intestinal infection called Clostridium difficile (C. diff) colitis, which is serious, but is rarely life-threatening.

While all risks to you may not be known, all attempts will be made to ensure your safety. You will be asked to return for scheduled study visits during which laboratory tests will be obtained to monitor your liver and kidney function along with blood counts. The study team will ask about any symptoms you have developed since your last study visit or any new prescribed or over-the-counter medications you are taking. You will have physical examinations at regular intervals and as needed.

In addition a data and safety monitoring board, which consists of a group of well-qualified individuals not associated with the study, will evaluate the data collected after half the subjects have completed the study. If this board feels that this trial should be discontinued, the trial will be stopped.

Rifaximin is not recommended for use during pregnancy as it may cause damage to the unborn baby. While you are on this study, you will be required to use some reliable method of birth control at all times. Women who are able to become pregnant will be tested periodically for pregnancy. If you become pregnant while on study you will stop the study product. We will continue to follow you throughout the pregnancy and immediately after pregnancy to see if there may be health problems related to the study medication. The only completely reliable methods of birth control are total abstinence or surgical removal of the uterus. Other methods, such as the use of condoms, a diaphragm or cervical cap, birth control pills, IUD, or sperm killing products are not totally effective in preventing pregnancy. Also, you may not breast-feed and be in this study.

Blood draws - The risks associated with a blood draw include bleeding, bruising, infection, and fainting. Infection, fainting, and related complications are rare. To reduce this risk, subjects will have their blood taken in the sitting position and will be monitored for 5 minutes after the procedure.

COLONOSCOPY – If you choose to have the colonoscopy you will need to go on a clear liquid diet, and take laxative medicines, to make you completely clear out any stool from your lower intestine, for about a day before the procedure. During a colonoscopy, a specially trained doctor (gastroenterologist) passes a colonoscope, which is a long, flexible, lighted tube, into your colon by inserting it through the rectum. The doctor inflates the colon with air and can see the inner lining of the colon by a tiny camera. During the colonoscopy, the doctor will remove up to 60 tiny pieces of tissue for study purposes. The gastroenterologist may also decide that, for medical reasons not connected to the study, they need to remove tissue and/or polyps for further examination, that would not be for study purposes. In this case, they will treat any problems through their office and not as part of this study. You will have this procedure described to you in greater detail before it is done, if you choose to have it.

The risks associated with colonoscopy include, but are not limited to, the following:

- Persistent bleeding after biopsy
- Peritonitis (a rare but potentially life threatening inflammation of the lining of the abdominal cavity)
- Perforation of the intestinal wall (rare, but potentially requiring emergency surgery for correction)
- Nausea, vomiting, bloating, or rectal irritation caused by the bowel cleanse prep and/or procedure
- Reaction to the sedative or pain medication, which is rare but may be serous

Certain factors or conditions may interfere with a colonoscopy. These factors include, but are not limited to, the following:

- Inadequate preparation of the bowel before the procedure
- Problems that may interfere with the procedure, such as narrowing of the colon, surgical adhesions, or disease, such as chronic inflammatory disease

In case one of the rare complications of colonoscopy occurs (such as perforation or peritonitis) you will need to be admitted to the hospital for evaluation and treatment.

Stored Samples

During your participation in this screening and on this study, blood will be collected by standard blood drawing techniques. We will also store some of your blood. These samples will be kept and used in future research to learn

more about HIV, the immune system and/or other medical conditions. Generally, the results from the research done with your stored samples will not be given to your private doctor and will not be put in your medical record. This is because the test results, unlike routine medical testing, may be experimental or preliminary. The relevance of these tests to your care may be unknown. However, at your request, the results of any research tests will be discussed with you or your physician by one of the investigators.

Labeling of stored samples

Your stored samples may be labeled with a code (such as a number) that only the study team can link to you. Any identifying information about you will be kept confidential to the extent permitted by law. Your stored materials will be used only for research and will not be sold. The research done with your materials may be used to develop new products in the future but you will not receive payment for such products.

Risks Associated with Stored Specimens

The greatest risk is the unplanned release of information from your medical records. The chance that this information will be given to an unauthorized person without your permission is very small. Possible problems with the unplanned release of information include discrimination when applying for insurance and employment. Similar problems may occur if you disclose information yourself or agree to have your medical records released.

Reasons for Withdrawal or Discontinuation

Your participation in this study is voluntary. You may withdraw at any time and for any reason. If you decide to discontinue participation, you will be invited to return for an end of study visit for clinical update and blood draw. You may be removed from this study, even without your permission if you miss appointments or if you do not comply with NIH and NIAID/Critical Care Medicine Department (CCMD) clinic and travel policies. If you withdraw your consent to allow sample storage, you will be removed from the study.

BENEFIT

You will not directly benefit from taking part in this study, but the information we learn may help us with the management of HIV positive patients in the future. This includes the availability of a drug that may control the chronic inflammation observed in this disease.

ALTERNATIVES TO PARTICIPATION:

This research study is not designed to treat any medical condition that you may have; you may choose to not participate in this study.

PAYMENT (COMPENSATION):

For taking part in this study, you will receive compensation based on time and inconvenience, according to NIH guidance. You will receive $40 per visit, and $350 for each colonoscopy. The total compensation for this study will range from $440.00 to do the minimum 11 study visits (and no colonoscopies) to $1490.00 if you participate in three colonoscopies and two additional blood draw visits

Genetic Testing

Some of the blood drawn from you as part of this study will be used for genetic tests. Genetic tests can help researchers study how health or illness is passed on to you by your parents or from you to your children. Some things to consider in thinking about whether or not to participate in these genetic studies include the possible effects on your

emotional wellbeing. In other words, how might you feel about yourself and your life if you learn information about risks that could affect your own health or that of your children? There may be no treatment for certain conditions and this may cause some individuals to feel anxious, depressed, or stressed. Additional genetics counseling and advice is available from the NIH to help you understand the nature and implications of findings about you and your family. Also, relationships with other family members may be affected by finding out risks they have but did not want to know. An example would be if your children, brothers, or sisters find out they have risks for health problems because of information found out about you. Genetic testing can also be used to determine if people are directly related. These tests can reveal that a person's biological parents are someone other than their legal parents. If these facts were not known previously, they could be troubling to learn. It is our policy to not discuss such information unless it has direct medical or reproductive implications for you or your family.

Some of the blood drawn from you as part of this study may be used for a test for HLA type, which is a genetic test of markers of the immune system. It is usually used to match bone marrow or organ transplants. For research, HLA testing might be used to try to identify factors associated with the progression of HIV disease or related conditions. In addition, determining HLA type is necessary to be able to perform certain research studies. Some HLA types have been associated with an increased risk of certain diseases like arthritis and other rheumatologic problems. However, simply having those HLA types doesn't mean you will develop these diseases.

By agreeing to participate in this study, you do not waive any rights that you may have regarding access to and disclosure of your records. For further information on those rights, please contact Dr. Frank Maldarelli, Principal Investigator at 301-435-8019]. Additional genetic counseling and advice are available from the NIH to help you understand the nature and implications of findings about you and your family. Any genetic information collected or discovered about you or your family will be confidential. Medical records containing this information will be kept under lock and key. We will not release any information about you or your family to relatives, any insurance company, or employer unless you sign a release requesting us to do so. Instances are known in which genetic information has been obtained or requested when a person applies for health insurance or a job. Genetic information can be requested and obtained when a person applies for health insurance or a job and has signed a release."

VOLUNTARY PARTICIPATION:

You may decide to be part of this study but you do not have to be in this study. Please do not sign the consent form until the Principal Investigator or one of his/her associates has adequately answered any and all questions you have about this study, your participation, and the procedures involved.

You may withdraw this consent at any time and discontinue further participation in this study without affecting your eligibility for care or any other benefits to which you are entitled. Should you choose to withdraw, you must contact the study team or a clinic representative. Please call 301-402-0980 Ext. 0 and ask for a member of the study team.
The investigator of this study may end your participation in this study at any time if he/she feels this to be in your best interest. If you are removed from the treatment part of the study, you will be asked to continue protocol visits for safety assessments completed by the study team.

The investigator may stop you from taking part in this study if:

- Being in the study is unsafe or dangerous to you
- You fail to comply with the requirements for being in the study
- The recommendations of the Data and Safety Monitoring Board (DSMB), a group of independent physicians and statisticians that will evaluate the study, may choose to stop the study after reviewing the data collected for safety or benefit reasons.

The sponsor of this study may end the study and/or your participation in this study for safety reasons.

NEW FINDINGS

If significant new findings develop during the course of this study that may relate to your decision to continue participation, you will be informed.

CONFLICT OF INTEREST

The National Institutes of Health reviews NIH staff researchers at least yearly for conflicts of interest. The following link contains details on this process http://ethics.od.nih.gov/forms/Protocol-Review-Guide.pdf. You may ask your research team for additional information or a copy of the Protocol Review Guide.

This protocol may have investigators who are not NIH employees. Non-NIH investigators are expected to adhere to the principles of the Protocol Review Guide but are not required to report their personal financial holdings to the NIH.

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.

Since this is a multicenter study your information may also be reviewed by the Uniformed Services University of the Health Sciences (USUHS) Infectious Disease Institutional Review Board (ID IRB), Infectious Disease Clinical Research Program (IDCRP), Walter Reed National Military Medical Center IRB, authorized members of the Regulatory Affairs Division of the Henry M. Jackson Foundation, and the University of Pittsburgh,

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, Frank Maldarelli Building 10 Room 5A06, Telephone 301-435-8019.

You may also call the Clinical Center Patient Representative at (301) 496-2626.

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 MAY 23, 2016 THROUGH MAY 22, 2017.

Signature of Investigator Date

Print Name

Signature of Witness Date

Print Name