INSTITUTE: National Institute of Allergy and Infectious Diseases

STUDY NUMBER: 15-I-0201 PRINCIPAL INVESTIGATOR: Alice K. Pau, PharmD

STUDY TITLE: Safety and Efficacy of Emtricitabine/Tenofovir Alafenamide as Part of Salvage Antiretroviral Regimens in Patients with Uncontrolled Viremia and Drug-resistant HIV Infection

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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 other 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 join 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 the NIH, or with family, friends, your personal physician, or other health professional. If you are signing for a child (younger than 18 years), then "you" refers to your child throughout this document.

## PURPOSE OF THE STUDY

You are invited to join this study because your HIV infection has been difficult to control with available medicines.

Antiretroviral therapy (ART) refers to a combination of drugs that are used for treating HIV infection. When ART drugs no longer work against the HIV virus, the HIV is said to have become "resistant" to the drugs. The HIV infection in your body may be resistant to many ART drugs. One drug that is often used to treat individuals with HIV infection is called tenofovir disoproxil fumerate or TDF. Some people have HIV infections that are resistant to TDF. Others cannot take TDF because they have kidney problems and taking TDF could cause damage to their kidneys.

In this study, we are testing a different form of tenofovir that may work with people whose HIV is resistant to TDF; it also

may be less damaging to kidneys. This new ART drug is called tenofovir alafenamide, or TAF. It is made by a drug company called Gilead Sciences. Currently, TAF is being studied in research trials for people with HIV or hepatitis B virus (HBV) infection. TAF is not approved by the Food and Drug Administration (FDA) outside of research studies. For this study, the FDA has allowed us to provide TAF in a combination pill with another ART drug called emtricitabine to people whose HIV infection cannot be successfully treated with other ART drugs. Emtricitabine has been approved by the FDA and is widely used for treating HIV infection. The combination pill is also called F/TAF.

We are inviting up to 20 volunteers to participate in this study. In addition to F/TAF, you will be prescribed other ART drugs that are FDA-approved. These drugs will be prescribed to you under the "DOTCOM" study (14-I-0009), in which you have already enrolled. We will evaluate your response to this ART combination and watch for side effects. If F/TAF works well for you, we will do our best to continue providing this drug to you until it is approved by the FDA and available in pharmacies.

## STUDY SCHEDULE

### Screening visit

If you agree to participate in this study, we will check your health with the following tests performed at the NIH:

- Physical exam with medical and social history
- Blood draws to check your HIV viral load and your health, and to see if you have hepatitis B infection
- Urine sample collection for kidney tests
- Pregnancy test (for women of childbearing potential)

If the results of these screening tests show that you are eligible for this study, your study team will construct a new ART combination that contains F/TAF with some new ART drugs, with or without some ART drugs that you are already receiving.

### Hospital stay

You will be hospitalized at the NIH Clinical Center for at least 10 days. For the first 9 days, you will take F/TAF along with your usual ART drugs. On the 10th day, we will give you a supply of F/TAF and some new ART drugs so you can take them at home. If you are able to stay in the hospital longer, you may choose to stay for 12 to 15 days.
On your first day in the hospital, we will do the following:

- Physical exam with medical and social history
- Blood draw to check your health and your HIV viral load (and your HBV viral load if you also have HBV infection)
- Urine sample collection for kidney tests
- Pregnancy test (for women of childbearing potential)
- Bone mineral density test (called a DEXA scan) – this can be done before, or within the first week of your stay

While you are in the hospital, we will draw blood from your arm approximately every other day to monitor your HIV infection. You will take ART drugs including F/TAF every day. We will tell you the schedule. It is important that you take your drugs on time every day. When it is time to take your ART drugs, you will need to ask a nurse to bring them to you. If 2 hours have passed and you still haven't asked for your ART drugs, then the study nurse will automatically bring them. This will happen each day that you are in the hospital. We will help you to manage side effects if you experience them. We will ask you about problems you have had taking your ART drugs in the past and discuss ways to help. This is called adherence counseling.

**Follow-up visits**
If you leave the hospital on Day 10, the results of your viral load tests will be available a few days later. If the tests show that F/TAF is not working for you, you will need to return to the NIH sometime between Day 12 and Day 15. You will be prescribed an ART regimen that does not include F/TAF and your participation in this study will be over. You may continue to participate in the DOTCOM (14-I-0009) study.

If F/TAF is working for you, you will take F/TAF plus your new ART drugs at home for as long as you are in the study. After your hospital stay, you will return to the NIH in 1, 2, 4, 8, and 12 weeks for follow-up visits. After your 12-week visit, you will come back about every three months. Follow-up visits will last about 2-4 hours and will include the following:

- Physical exam with medical and social history
- Adherence counseling
- Blood draw to check your health and your HIV infection
- Urine sample collection for kidney tests
- Pregnancy test (for women of childbearing potential)
- DEXA scan (at two follow-up visits only)

If you do not have a good response to the ART, the study team may design a new combination for you. You may have to come back to the NIH so that we can change one or more of your ART drugs. Even if the new combination does not include F/TAF, you will still be followed under this protocol.

After about 1 year, you will be finished with this study. We expect F/TAF to be available as a prescription drug by this time. If it isn't, and if it is still under development by Gilead, we will invite you to continue participating in this study.

**Unscheduled visits**
You should return to the NIH as needed if you have any problems. Blood may be drawn at these unscheduled visits.

## STUDY PROCEDURES AND RISKS

**Study drug (F/TAF):** We will provide you with emtricitabine 200mg/tenofovir alafenamide 25mg oral tablets. You will take one tablet per day. You will also receive other ART drugs prescribed for you.

The most common side effects associated with F/TAF are headache, diarrhea and nausea. Less common side effects are vomiting, fatigue, rash, stomach pain, indigestion and gas. F/TAF must be stopped if your blood tests show too much acid in the blood (lactic acidosis) – this side effect is rare. If you also have HBV infection, it's possible that F/TAF can cause the hepatitis infection to worsen at first. If you stop taking this study medication without other therapy your hepatitis B infection can also worsen. Your doctor will follow your HBV status and liver function closely. There may be other side effects from F/TAF that we do not know about yet. You will be followed closely and treated for side effects as necessary. F/TAF has been given experimentally to more than 1,000 patients with HIV infection. Some of these patients had kidney problems or hepatitis B infection before they started taking F/TAF. Most patients who took F/TAF in these studies were able to tolerate the drug and to manage their HIV infection. One pregnant woman taking F/TAF had a miscarriage and her doctor thought it could be related to F/TAF. There have not been enough studies in pregnant women to know if all HIV drugs are safe to take during pregnancy. Therefore, you will not be allowed to begin this study if you are pregnant. If you are able to become pregnant, then you must agree not to have sex or to use contraception when you begin the

study. Because of the risks of HIV transmission to the newborn, serious drug reactions, and the development of viral drug resistance in the newborn, mothers should not breastfeed while being treated with F/TAF.

It is important that you tell the study team about any medicines or supplements you have been taking. While you are taking F/TAF, you must avoid the following drugs and supplements: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, bisphosphonate, St. John's wort, echinacea, milk thistle, sho-saiko-to, and probenecid.

**DEXA scan:** This is an x-ray that measures how much calcium and other types of minerals are in the bones of your lower spine and hips. TDF may increase the risk of bone fracture in some patients; we do not know if TAF will also have this effect. The DEXA scan helps to predict your risk of having a bone fracture in the future. For the scan, you will lie on a soft table while the scanner passes over your lower spine and hip. This will take about 5-10 minutes, and it is painless.

The main risk from an x-ray is the increased lifetime risk of cancer due to radiation exposure. This radiation exposure is not necessary for your medical care and is for research purposes only. The amount of radiation you will be exposed to from the 3 scans planned for this study is 0.00024 rem for adults or 0.00012 rem for children (<18 years). This is below the limits set for research participants by the NIH Radiation Safety Committee, which are 5 rem for adults and 0.5 rem for children. For comparison, the average person in the United States receives a radiation exposure of 0.3 rem per year from natural background sources, such as the sun, outer space, and the earth's air and soil. Therefore, the dose that you will receive from this research study is much less than the amount you would normally receive in a year from these natural sources. If you would like more information about radiation and examples of exposure levels from other sources, you may ask for a copy of the pamphlet "An Introduction to Radiation for NIH Research Subjects".

A fetus is more sensitive to radiation than adults or children. Women of childbearing potential will have a pregnancy test before each DEXA scan. If you are pregnant, you will not have the DEXA scan.

**Physical exam with medical and social history:** You will undergo a physical exam. We will ask you questions about how you are feeling, if you've had any recent illness, and about the medications you are taking now and have taken in the past, including non-prescription drugs. We may also ask you questions about your social life, such as whether you drink alcohol or use recreational drugs, and whether you are sexually active.

**Blood draw:** Blood will be collected to measure your HIV viral load, blood cell counts, and to see if your liver and kidneys are working well. Some blood will be used to test for hepatitis, and to see if your HIV has resistance to ART drugs (genetic testing of the virus). Blood may also be used for genetic testing. The total amount of blood drawn for research purposes will be within the limits allowed by the NIH Clinical Center. The risks related to drawing blood from a vein in your arm include pain, bruising, lightheadedness, fainting and, rarely, infection at the site where the needle entered your arm.

**Hospital stay:** You may become bored or restless during your hospital stay. You will have access to game rooms, television, wireless internet access, a patient library, and a fitness center. You may receive visitors. You may request a pass to leave the hospital during the day.

## BENEFITS

You may benefit from taking the study drug and the new ART combination, as well as from the care you will receive during the study. However, there is no guarantee that the study drug and the new ART combination will manage your HIV infection. Your participation may help us better understand how to treat HIV infection in the future.

## ALTERNATIVES TO PARTICIPATION

You can choose not to participate in this study. This decision will not affect any ongoing care or evaluations you may be receiving at the NIH. Your eligibility to participate in other research studies at the NIH will not be affected by your decision to enroll or not enroll in this study.

## WITHDRAWAL FROM THE STUDY

You can stop participating in this study at any time. The decision to no longer participate in this study will in no way affect your ability to receive care at the Clinical Center or to participate in other NIH studies. You may be removed from the study without your consent if you miss your scheduled appointments, refuse to follow the study procedures, or if the study doctor believes that continuing the study drug would be harmful for you.

**You should not stop taking your study drugs without first talking to a member of the study team.** If you stop taking the study drugs early, we will ask you to return to the NIH for monthly safety tests for about 3 months after you stop. If you don't want to return to the NIH, we will ask you to follow up with your primary care doctor.

## COMPENSATION

You will not be paid for participating in this study.

## COSTS TO YOU FOR YOUR PARTICIPATION

There will be no charge to you or your health insurance company for any of the tests, procedures, or medications that are directly related to this study. We will provide you with ART drugs throughout the study. If TAF is available for sale at the end of the study, you may be able to obtain it through the DOTCOM protocol. After you have finished participating in this study and in the DOTCOM protocol, you will be asked to obtain your ART drugs from sources other than NIH Clinical Center. Our social worker can assist you with this as necessary.

## NEW FINDINGS

Any new findings discovered during this study that are considered relevant to your health or to your decision to continue participation will be discussed with you.

## STORED SAMPLES AND FUTURE RESEARCH

If you agree to participate in this study, you also agree to let us store some of your blood samples for future research to help us learn more about treating HIV infection. The samples will be labeled with a code that only the study team can link to you. Any information that can be traced back to you will be kept as private as possible. If you change your mind and decide you do not want us to store your samples, please contact us. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy all of your samples.

Your coded samples might be sent to other investigators for their research. Other information, such as your sex, age, health history, or ethnicity might also be shared. Your samples will not be sold, and you will not be paid for any products that result from this research. Future studies may require health information about you, such as your present health status, which we might not already have. If so, our study team may contact you. Future research that uses your samples will not help you, but it may help us learn more about HIV. In general, the research tests performed in this study are not like routine medical tests, and they may not relate directly to your medical care. The greatest risk of allowing us to store your samples will be an unplanned release of your identification from the samples due to release of this information from the stored sample database. The chances of this happening are very low.

**Genetic testing:** Your stored blood samples may be used to conduct genetic tests in the future. These tests would help us to better understand how genes may contribute to HIV drug resistance. Genetic tests can provide a lot of detailed information about a person's genes. However, we often do not know what this information means, so we may not have anything to tell you about the results. If we were to find a genetic testing result that we thought was urgent to deal with because of your health, we would confirm the result and then tell you about it. We expect this sort of situation to be very unlikely. Genetic tests done in a research lab from your stored blood samples will not become part of your medical record. Any genetic information collected from or discovered about you will be kept confidential.

Some of the blood drawn from you during this study will be used to test for HLA type, which is a genetic test for markers of the immune system (body system that fights off disease). Some people with a particular kind of HLA gene have a bad reaction to the ART drug abacavir. We will do the HLA test to find out if we can prescribe abacavir to you. Results from the HLA test will become part of your medical record at the NIH. Medical records containing this information are kept in a secure place.

## CONFLICTS OF INTEREST

The National Institutes of Health reviews NIH staff researchers at least yearly for conflicts of interest. You may ask your research team for additional information or for a copy of the "Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Clinical Research at NIH". This protocol may have investigators who are not NIH employees. Non-NIH investigators are expected to adhere to the principles of the 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.

**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. For this protocol, the compensation plan is outlined above.

**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 Alice Pau, PharmD, Building 10, Room 11C103, telephone: 301-451-3740; or the study coordinator, Alexander Ober, BSN, telephone: 301-435-7912.

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 SEPTEMBER 2, 2015 THROUGH SEPTEMBER 1, 2016.**

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____