A Retrospective/Prospective Study to Assess Safety, Tolerability, and Efficacy of Sofosbuvir based Direct Acting Antiviral (DAA) Therapy for Hepatitis C Treatment in HIV/HCV Coinfected Subjects Pre or Post Liver Transplant

INFORMED CONSENT: PROSPECTIVE SUBJECTS

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PROSPECTIVE ARM

A Retrospective/Prospective Study to Assess Safety, Tolerability, and Efficacy of Sofosbuvir based Direct Acting Antiviral (DAA) Therapy for Hepatitis C Treatment in HIV/HCV Coinfected Subjects Pre or Post Liver Transplant

CONSENT VERSION 3.0 /July 11, 2017
PROTOCOL VERSION 3.0 / July 11, 2017

[NOTE: Site specific sections are identified in bold italics, and will be tailored at each center accordingly]

INTRODUCTION

We invite you to take part in a medical research study at the ***[NAME OF CENTER].*** Your study doctor(s) **[NAMES, MD]** from the **[NAME OF CENTER]** will explain the study to you.

First, we want you to know that:

Taking part in this 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.

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 ***[NAME OF CENTER]*** doctors or research team before you agree to the study.

A description of this clinical trial will be available on http://www.Clinicaltrials.gov. 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.

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 ***[NAME OF CENTER],*** or with family, friends or your personal physician or other health professional.

Study Team

Your study team consists of doctors, nurses and other specialized medical professionals, who are experienced in taking care of patients with hepatitis C virus (HCV). You will be interacting with some if not all of the study team members at specific study visits. However, a study team member will always be available to you if you have a question about the study, your response to treatment, or the study drugs.

Why is this study being done?

You are being asked to participate in this study because you have HIV infection and you have liver disease caused by infection with HCV. Your blood tests show that the HCV infection continues to be present (i.e., the virus continues

to reproduce), causing a chronic infection. Currently there are about 4 million people with HCV in the US and only about 10 – 20% are being treated for their HCV, many with severe or advanced liver disease. In your case you have been diagnosed as having severe liver disease and your HCV virus is still active.

Sofosbuvir (SOF) and ledipasvir (LDV) are combined in one pill called HARVONI that is now approved in the US for the treatment of chronic hepatitis C genotype 1 infection in adults. This study will also enroll participants with genotypes 1, 4, 5 and 6. The safety, tolerability and efficacy of SOF/LDV have not been established in patients with decompensated cirrhosis (clinical evidence of cirrhosis such as internal bleeding, fluid in the belly, or yellowing of the eyes and skin) or after liver transplantation. The purpose of this study is to determine whether SOF/LDV in combination for 12 to 24 weeks can be safe, tolerated and effective for treating HCV infection before or after liver transplantation in people who also have HIV infection. This drug works by blocking the HCV from dividing in your body.

How many people will take part in the study?

This study will enroll 10 - 20 participants with HIV infection who also have HCV infection with severe liver disease or who have had a liver transplant. Participants will receive 12 weeks of SOF/LDV (up to 24 weeks for pre liver transplant participants and for people who have had a liver transplant and now have cirrhosis). SOF/LDV for 12 weeks has been shown to be effective in HCV patients with HIV with high cure rates. Rates of cure were slightly lower in people who had failed previous HCV treatment or had cirrhosis. Increasing SOF/LDV therapy from 12 to 24 weeks increased the cure rate in prior studies.

The drug will be provided by the manufacturer, Gilead Sciences, Inc. You will be followed during the treatment and for 24 weeks afterwards. After starting the study drugs, if you have to stop them for any reason, you will be offered treatment with an effective regimen based on prior response to the treatment, whether the HCV has become resistant or not, and other factors.

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

Your participation in the study involves multiple visits to the ***[name of center]*** over a period of up to 1 year from the start of study treatment. In general, each visit will require collection of blood to be used for safety labs (blood counts, blood clotting tests, kidney function, muscle and liver tests, blood minerals, and electrolytes), as well as labs to determine the amount of HCV in your blood (HCV viral load), and levels of SOF/LDV. Your weight will also be measured at all main study visits. All these tests are routinely performed for the care of individuals with chronic HCV or HIV infection or who have had a liver transplant.

Participation in this protocol might affect the timing of liver transplantation if you have not had one yet. If a liver becomes available before you have completed therapy, your physician will discuss with you the best course of action and you will collectively decide how to proceed.

Study Drugs

The study drugs include SOF/LDV. These are given as a single combination pill each morning either with or without food. The pill includes 400mg of SOF and 90mg of LDV. Because we will check the levels of the study drugs in your blood during your visits, we ask that you wait until after your blood is drawn to take your dose on study visit days. We will supply enough study drugs at each visit to last until your next visit.

Other Medications

You will continue to take all the other medication prescribed by your doctor during the study. They will be reviewed during the screening visit and approved if you are eligible for the study. It is extremely important to provide an accurate list of all your medications (prescribed, over-the-counter, and herbal) at each visit, or if there are changes between visits, so that we can determine if there is an interaction between any of your medications and the study drugs. However, we will not supply other medications.

Before you begin the main part of the study…

During screening, you will review this consent prior to any study procedures. After the consent is signed, your medical

history, allergies, and medications will be reviewed with a nurse. You will have laboratory tests done to help determine your eligibility (unless completed within the last 8 weeks). Some of the blood will be obtained to study the immune response to HCV, and it will be stored for possible evaluation of the HCV resistance to antiviral medications. Some labs will be done to evaluate your liver disease and to help determine whether HCV is the only cause of your liver disease. Urine testing will be done. You will have a physical examination and your weight measured and your medical history will be reviewed by a doctor, physician assistant or nurse practitioner.

The severity of your liver disease must be documented by standard of care method prior to enrollment. This may involve a liver biopsy or transient elastography (FibroScan®) if you have not had one performed within 12 months. We will explain in great detail the process it involves, and the risks it may also present. You may have a liver ultrasound or other imaging done prior to the liver biopsy if the study doctor feels it is necessary. At the time of liver biopsy, you will sign another consent that will explain the procedure and risks in greater detail.

During the main part of the study…

Day 0 (Start of SOF/LDV)
On this day you will have a physical examination and your vital signs will be taken. Blood will be drawn for standard of care labs, including blood drawn to measure the amount of HCV in your blood (HCV viral load). Blood will also be drawn for HCV and immunology research purposes. If you are a female of childbearing potential, you will have a pregnancy test. You will then receive your first dose of SOF/LDV (which are given in one pill). You will receive teaching about the study drugs.

Other Visits: Week 4, and 12 (+ weeks 24 for those receiving 24 weeks of treatment)
These visits are aimed at determining how well the study drugs are reducing HCV viral load and how you are tolerating them. Blood tests as noted above (e.g., safety labs, viral loads, study drug levels, and immunology studies) will be done, and your weight will be measured at all study visits. At week 4 and week 12 or 24 (when you stop taking the study medication) you will have a physical exam with a medical provider in addition to having labs collected and potential side effects reviewed. The last dose of study medications will be taken after receiving them for 12 or 24 weeks.

End of Treatment Visit Week 12 (or Week 24 for those receiving 24 weeks of treatment)

You will have a liver biopsy performed at the end of treatment as part of standard of care. If you do not have a liver biopsy performed as part of standard of care, you will have liver staging performed by another method, which may include a FibroScan®.

HCV Viral Load Results from Week 4
By Week 4 on treatment, if you do not have a significant drop in your HCV viral load you may be discontinued from therapy. If you are discontinued from treatment, you will be advised of your options. If you were to continue to take the study drugs you would have a risk of becoming resistant to this drug or other similar drugs. If you stop study medications early you will continue to be seen every 12 weeks for safety monitoring and may complete the week 12 labs and procedures as an end of treatment visit.

Other
If you have not yet had a liver transplant when you start taking the study drug to treat your hepatitis C, we will collect some of the tissue from your liver when we remove it for transplant. The tissue will not be used to make clinical decisions about your care. The study investigators would like to see if they can detect the hepatitis C virus in the liver when it is removed, even if you have been treated and have an undetectable amount of hepatitis C virus in your blood. This is solely for research purposes. It is possible that some of this tissue will be made available to researchers outside of this study. If so, it will be done in a way that will not identify you.

When you are finished receiving study drug (SOF/LDV)…

Follow up post treatment month 3 and month 6
You will be asked to return for blood tests, blood draw for research purposes, weight measurements, and routine clinic visits. During the last visit, the results of the study will be discussed with you and as your results are available someone from the study team will keep you up to date on the status of your HCV infection after treatment.

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

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or serious. You should talk to your study doctor about any side effects you experience while taking part in the study

Side Effects of SOF/LDV

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects, but includes the more common side effects with a known or possible relationship. If you have questions concerning study drug side effects please ask the medical staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study drug and also before starting any new medications while in the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while in this study.

In studies, this drug has been generally well tolerated. Risks and side effects related to SOF/LDV include:

Most Common

- Tiredness
- Headache

Less Common

- Nausea
- Diarrhea
- Insomnia
- Cardiac disorders when co-administered with amiodarone

Resistance

We do not know how effective SOF/LDV will be in eliminating HCV in people with HIV. This is one of the purposes of our study. One of the main risks of participating in this study is the possibility that HCV may become resistant to the medication and may limit your future treatment options. The likelihood of resistance developing is higher if you skip doses or do not follow the study recommendations. If you show possible resistance to the study drugs by having an increase in your HCV viral load while on treatment, you will be asked to return to repeat the HCV viral load test quickly, and will be taken off the SOF and LDV if the repeat test shows the same. You will still be followed for the study but less frequently (every 12 weeks).

If you do not respond to treatment with SOF/LDV there is a potential risk of not being able to respond to other drugs in the same class (that are being developed) in the future. However this should not affect how you respond to other available treatments such as interferon, RBV and HCV protease inhibitors.

HIV Virologic Rebound

If you are on HIV medicines and during treatment your HIV viral load reaches more than 1000 copies/mL, we will ask you to come back to repeat the test and check for resistance to your antiretroviral drugs. If resistance is detected, you may be asked to switch to a different combination of HIV medicines or possibly the study doctor may ask you to hold off taking HIV medicines until you finish taking the HCV study drugs.

Potential Risk of Kidney Problems

In participants on HIV medicines that contain tenofovir, there is a possibility that the drug levels might be raised to higher than normal levels. Because of this, all participants on study will receive increased monitoring of kidney function. This will be done through blood and urine testing during study visits. If this would happen, a study doctor would explain it to you and it is possible that the dose amount of your HIV medicine may have to be adjusted or stopped.

Liver Biopsy

Doctors who specialize in this procedure, Interventional Radiologists, will perform the liver biopsy. The liver biopsy will be done as an outpatient procedure and you will need to have someone come to the procedure to accompany

you home. As a precaution, we will ask you to remain in the hospital for at least 6 hours after the procedure to be observed and evaluated for any possible complications from the procedure. We will try to make the experience as comfortable for you as possible. We try to make you sleepy by giving you a medication called Versed (midazolam) through an intravenous line (a line that goes into your vein) before the process. A numbing medication called Xylocaine (lidocaine hydrochloride) is injected under your skin to make the area numb before a larger needle is put through to do the biopsy. The medications mentioned above are safe at the doses that they will be used. However, in rare incidences, you may have an allergic reaction to them. The doctors who will do the liver biopsy will use an ultrasound scan to locate your liver and a needle to get some small pieces of your liver. However, occasionally a liver biopsy can cause problems such as bleeding and infection. Rarely, the biopsy needle misses the liver and can hit another organ and cause damage to that organ. If the problems of bleeding, infection, and organ damage are very serious, it may very rarely result in death.

FibroScan®

The FibroScan® technique will be used to measure the amount of liver fibrosis in a non-invasive and painless manner. Performed at the bedside in the clinic, a machine will generate a pulse wave at the skin surface, which will spread through the liver. The speed of the wave will be measured by ultrasound. In general, the whole examination process can be completed within 15 minutes.

This Fibroscan will be performed by technical personnel and/or hepatologist and the results will be reported to the investigators. There are no potential discomforts or risks involved with the Fibroscan procedure. However, according to the recommendations of use and based on safety and efficacy matters; pregnant women, patients with ascites (fluid in the abdomen), persons with active implantable medical devices and persons with a waist size more than 100cm will be excluded from this procedure.

Pregnancy/Birth Control

No adequate human data are available to establish whether or not SOF/LDV poses a risk to pregnancy outcomes. Animal studies have not found a risk to the fetus, but there are no well-controlled studies in pregnant women. Women of child bearing potential must have a negative urine pregnancy test on the day study drug is started.

If you become pregnant during the study, it is important that you tell us right away. You may need to stop taking the study drugs, but we will continue to follow you and the outcome of the pregnancy.

Blood Drawing

The potential risks of the needle stick to draw blood include pain, bruising, bleeding, fainting, and infection. Discomfort from this procedure is generally short lasting, and serious side effects are extremely rare. Some people experience feelings of lightheadedness or dizziness after having blood drawn. The amount of blood drawn will be within the limits allowed for adult participants.

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 learn about potential relationships between response to HCV treatment and genetic factors. HLA testing may also be completed. This is a genetic test of markers of the immune system. It is usually used to match bone marrow or organ transplants. 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 For research, HLA testing might be used to try to identify factors associated with the progression of disease or related conditions. In addition, determining HLA type is necessary to be able to perform certain research studies.

Results of HLA testing may become a part of your medical record if done outside of the study requirements, but will be confidential. Records containing this information will be kept on password-protected computer systems and in locked and secured quarters within the hospital. We will not release any information about you or your family to relatives, any insurance company, employer, or your primary care physician without your written permission. There may be a risk that genetic information obtained as a result of participation in research could be misused for discriminatory purposes. However, state and federal laws provide some protections against genetic discrimination. Researchers who will have access to genetic information about you will take measures to maintain the confidentiality of your genetic information. Although we are committed to confidentiality, a court could still subpoena your medical records. All of

these issues should be carefully considered before joining the study.

Are there benefits to taking part in the study?

SOF/LDV (combined in one pill called Harvoni), is approved for the treatment of chronic HCV. The safety and efficacy of Harvoni has not been established in people with decompensated cirrhosis or in people after liver transplantation. The information from this study may help the researchers learn more about SOF/LDV in the treatment of people with HCV and HIV that are pre or post liver transplant. It is possible that you would receive no benefit from the study treatment and possible that you may effectively treat your HCV and no longer have chronic HCV after completion of the study treatment.

What other choices do you have if you do not take part in this study?

We encourage you to discuss this study with your physician and to explore other treatment options. Other treatment options for chronic HCV infection include other oral combinations of medications or choosing not to pursue treatment of HCV at this time.

Can you stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely. It is important to tell the study doctor if you are thinking about stopping so that your doctor can evaluate any risks and discuss what alternative follow-up care and testing could be most helpful for you.

Reasons for Stopping Study Medications

If you are not responding to the study medications (checked frequently by measuring the levels of HCV in your blood) or develop a potential life threatening complication from the medication, we will stop the study medications completely. However, you will still be followed but less frequently (every 12 weeks). Regardless of the stage of liver disease, the recommendations are to treat HCV if medically possible, however some physicians might choose to wait and not treat in the immediate future.

Reasons for Withdrawal or Study Discontinuation

Your involvement in this study is entirely up to you. You may leave the study at any time and for any reason. If you decide to leave, we may ask you to return for a final visit to perform tests and exams to ensure safety. However, you will not be required to return for this visit.

You may be discontinued from the study (taken off the study without our asking for your permission) if:

- You become pregnant while undergoing treatment with SOF/LDV.
- We cannot locate you, or if you miss multiple visits or study drug doses.
- You develop a condition that it is life threatening or any other significant risk as judged by the Investigator.
- We or your primary care provider believe that it is in your best interest to stop taking the study medications even if the criteria required for stopping treatment have not been met.
- Either SOF or LDV are no longer produced by the company, or if a decision is made to stop the study.
- Refusal to have your samples stored will be treated as a withdrawal of consent and you will be removed from the study.

What are the costs of taking part in this study? [Excluding NIH Clinical Center]

The costs of all visits and tests described above will be billed to you or your insurance carrier, with the exception of the optional non-standard of care research biopsy, the blood draw for research purposes, and the study drug, which will be paid for by the study sponsor. Insurance companies and other carriers sometimes refuse to pay the costs of treatment when individuals are participating in research. If this happens in your case, you will be billed for the care your insurance will not cover. Financial counselors are available through the hospital accounting department to discuss this with you.

Will you be paid for taking part in this study?

You will not be paid for participating in this study. If you are injured as a result of being in this study, **CENTER NAME** will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs. **CENTER NAME** and the U.S. National Institutes of Health (NIH) do not have a mechanism to provide compensation for research related injury. For further information about this, you may call **XXX** at **XXX- XXX-**

XXXX.

What are your rights if you take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits to which you are otherwise entitled. Refusal to participate will not affect your legal rights or the quality of care that you may receive at this center.

You will be informed by the research team if any important new findings develop during the course of the study that may affect your decision to continue.

Who can answer your questions about the study?
You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor(s) **[name(s)]** at **[telephone number(s)]**

Stored Samples and Future Research
If you agree to participate in this study, you also agree to let us store your samples for future research. These stored samples may help us learn more about HCV. We will label your stored samples with a code that only the study team can link to you. We will keep any information that can be traced back to you 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 your samples.

We might send your samples to other investigators for their research, without any information that can identify you. We might also share information such as your sex, age, health history, or ethnicity. We will not sell your samples and you will not be paid for any products that result from the research. Some future studies may need health information (such as smoking history or present health status) that we don't already have. If so, our study team will contact you. Future research that uses your samples will probably not help you, but it may help us learn more about how to treat or prevent HCV and other health problems. In general, the research tests we perform are not like routine medical tests, and may not relate directly to your medical care.

How will information about you be kept confidential?
Your medical records will be kept confidential to the extent allowed by the law. Your name or any other data that might identify you will not be used in any reports or publications resulting from this study. Because of your consent to participate, your medical records may be reviewed by NIH staff, by the study Sponsor and by the IRB (the body responsible for making sure that the study follows the guidelines for the protection of human research subjects) with the understanding that these records will be used only in connection with carrying out obligations relating to this clinical study. We will be routinely supplying information about you to your personal physician(s). You may change physicians whenever you like, but we need to have a physician with whom we can communicate about you. We would not ask your permission for each of these contacts.

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/procedures.htm#protocol. 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 **[and name of center]** 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, we 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 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 members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. **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, ***[Henry Masur MD (NIH) , Telephone: XXXX or Peter Stock MD (UCSF) at XXXXX, or Site PI (Center Name). You may also call the Clinical Research Center Patient Representative at (301) 496-2626 at the NIH or XXXXX (non-NIH centers)]***

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

CONSENT

You have been given copies of the signed and dated consent form and the Experimental Subject's Bill of Rights to keep.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in the study without jeopardy to your medical care. To participate, you should sign below.

_____

Name of Participant

_____ _____

Signature of Participant Date

_____

Name of Person Obtaining Consent

_____ _____

Signature of Person Obtaining Consent Date