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

PROTOCOL

VERSION 3.0 July 11, 2017

Study Sponsor(s):	The National Institute of Allergy and Infectious Diseases (NIAID)
NIAID Funding Mechanism:	*U01*
Clinical Trial Phase:	Phase IV (non-IND)
Study Drug Provider:	Gilead Sciences
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Version of Protocol – DAIDS-ES 12044 (STOP-CO)

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Roles and responsibilities of study team at NIH (CCMD/NIAID) on this U01 Project

Henry Masur, MD is the NIH Intramural Principal Investigator and will oversee the protocol and all the individuals working on it at The NIH Clinical Center. These individuals will be listed on the NIH Protocol Application as Associate Investigators; and may include federal employees, special volunteers, and/or contractors. Dr. Masur will be authorized to obtain informed consent, have access to identifiable data, and participate in data analysis and manuscript preparation/review.

The Lead Associate Investigator at NIH will directly oversee the protocol subjects admitted to the clinical center for pharmacokinetic and viral kinetic monitoring, as well as participate in monitoring of patient safety, take routine calls regarding safety and event reporting with the extramural investigators, obtain informed consent, have access to identifiable data and participate in data analysis and manuscript preparation/review.

Associate Investigators at the NIH will see protocol subjects during outpatient and inpatient visits, participate in monitoring for patient safety, take routine calls from subjects, obtain informed consent, have access to identifiable data and participate in data analysis and manuscript preparation/review.

The study coordinator/nurse will also be authorized to obtain informed consent, have access to identifiable data and may participate in manuscript preparation/review.

Mary Hall will provide regulatory support for the NIH site. She will not obtain informed consent but may have access to identifiable data.

Michael Proschan, PhD is the NIAID biostatistician who wrote the statistical section of the protocol. He will have access to identifiable data and participate in data analysis and manuscript preparation/review.

PROTOCOL SIGNATURE PAGE

Protocol:	**Version/Date:**
STOP-CO	Version 3.0/July 11, 2017

Title:

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

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

_____

Site Principal Investigator Name (Print)

_____ _____

Site Principal Investigator (Signature) **Date**

TABLE OF CONTENTS

ABBREVIATIONS

AA	African American
AE	Adverse Events
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AUC	Area under the curve
BMI	Body mass index
CHC	Chronic hepatitis C
DAA	Direct acting antiviral
ECG	Electrocardiogram
ESA	Erythropoiesis stimulating agent
ETR	end of treatment response: <LLOQ HCV RNA at the end of treatment
EVR	early virologic response: <LLOQ HCV RNA or 2-log decline at Week 12 (partial EVR)
FDA	Food and Drug Administration
FDC	Fixed dose combination
G-CSF	granulocyte colony stimulating factor
GT-1, -2, and -3	Genotype 1, 2, and 3
HBV	hepatitis B virus
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
IL28B	Interleukin 28B
IFN	interferon
IRB	Institutional Review Board
ISG	interferon-stimulated gene
LDV	Ledipasvir
LI	Lead investigator
LOD	Level of detection
LLOQ	Lower Level of quantification
MELD	Model for End-Stage Liver Disease
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PBMC	peripheral blood mononuclear cell
pegIFN	Pegylated Interferon
PI	principal investigator
sofosbuvir	sofosbuvir
QWBA	quantitative whole-body autoradiography
RBV	ribavirin
RVR	Rapid virologic response; <LLOQ HCV RNA at Week 4
SAE	Serious adverse events
SOC	Standard of care
SOF	Sofosbuvir
SVR	sustained virologic response <LLOQ HCV RNA at 24 weeks (or 6 months) after the end of treatment
TVR	Telaprevir

PROTOCOL SUMMARY

Full Title:	A Retrospective/Prospective Cohort 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
Short Title:	Sofosbuvir based DAA therapy in HIV/HCV coinfected pre or post liver transplant
Study Name:	STOP-CO
DAIDS ES #:	12044
Clinical Phase:	Phase IV
Sample Size:	10+ prospective (up to 20) 40+ retrospective
Accrual Period:	12 months
Study Population:	HIV+ Adults with decompensated liver disease pre or post liver transplant with chronic hepatitis C virus (HCV) infection
Participating Sites:	Enrolling Centers: University of California, San Francisco, Mt. Sinai Medical Center, Columbia University, and University of Pennsylvania, University of Maryland, Georgetown University, Johns Hopkins University; Collaborating Center: NIH Clinical Center.
Study Design:	Retrospective/Prospective, open-label study using sofosbuvir based DAA therapy to treat HIV/HCV coinfected pre or post liver transplant participants
Primary Objectives:	1. To assess the safety, tolerability, and efficacy of sofosbuvir based DAA therapy for 12 - 24 weeks in HIV/HCV coinfected participants pre- and post-liver transplant. 2. To assess the safety, tolerability, and efficacy of a fixed dose combination (FDC) of sofosbuvir and ledipasvir (SOF/LDV) for 12 - 24 weeks in HIV/HCV coinfected participants pre- and post-liver transplant

Secondary Objectives:

1. To evaluate changes in HCV viral kinetics with fixed dose combination (FDC) SOF/LDV or sofosbuvir based DAA therapies in HIV/HCV coinfected subjects with pre or post liver transplant HCV

2. To evaluate the proportion of subjects with HCV viral loads below the level of quantification at various time points of the study

3. To determine sustained virologic response rates with FDC SOF/LDV or sofosbuvir based DAA therapies.

4. To identify the determinants of response to interferon sparing therapy in eradicating HCV in pre or post liver transplant HIV/HCV coinfected subjects

5. To identify the host genetic, protein, gene, and proteomic factors that are associated with responses to interferon (IFN) sparing therapy in pre or post liver transplant HIV/HCV coinfected subjects (*prospective arm only*)

6. To determine if levels of interferon-stimulated genes (ISG) expression in PBMCs or liver can predict rapid virologic response (RVR), end treatment response (ETR), and sustained virologic response (SVR) in subjects receiving IFN sparing therapy (*prospective arm only*)

7. To evaluate the proportion of subjects whose ALT normalizes during therapy and between baseline and SVR

8. To evaluate the emergence of viral resistance during therapy with FDC SOF/LDV or sofosbuvir based DAA therapies.

9. To evaluate change in liver fibrosis and liver function before and after treatment with FDC SOF/LDV or sofosbuvir based DAA therapies.

PRÉCIS

Liver transplantation (LT) in HIV/HCV patients results in worse outcomes than in HCV or HIV patients [1-4]. Similarly, survival rates after LT are significantly lower in HIV/HCV patients than HCV patients [1, 2, 5, 6]. While 1- year and 3- year survival rates in HCV monoinfection are reported at 76-92% and 72-79%, rates with HIV and HCV coinfection are reported at 67-88% and 56-62%. Spontaneous HCV clearance after LT is rare and reinfection with hepatitis C after liver transplantation is nearly universal. Post-transplant hepatitis C is a common problem in the management and survival of HIV/HCV coinfected patients after liver transplantation. HCV treatment is often initiated after LT to remove the viral antagonist prior to further disease progression or decompensation. Rates of sustained virologic response to treatment with interferon (IFN) and ribavirin (RBV) after liver transplantation are low (around 14.8%). Moreover, overlapping toxicities between antiretrovirals (ARVs) and interferon/ribavirin can cause toxicities in coinfected patients that require treatment cessation, ultimately leading to fewer patients who are able to complete treatment.

Recently, several trials have confirmed the efficacy of potent direct acting antiviral (DAA) therapy without concomitant IFN in the treatment of HCV. One such drug has been sofosbuvir, an NS5B inhibitor which in combination with IFN-based or IFN free regimens in several trials [7-9] has been highly effective. In HCV infected pre transplant subjects, the use of sofosbuvir and ribavirin treatment prior to transplantation prevented HCV recurrence in the majority of subjects who had HCV RNA suppressed for at least 4 weeks prior to transplant [10]. In subjects who developed recurrent hepatitis C post-transplant, the use of sofosbuvir and ribavirin showed promising early results with over 70% of subjects achieving early sustained virologic response (SVR) [11]. More recently, the use of fixed dose combination (FDC) sofosbuvir-ledipasvir with or without ribavirin has been shown to be effective in HCV monoinfected subjects including cirrhotics with SVR rates of at least 95%. [12, 13] [14, 15] Drug interaction studies have been completed with several HIV antiretrovirals and treatment trials of SOF/LDV in HIV/HCV coinfected subjects have been initiated. Hence, an ideal regimen to treat this difficult patient population will be an interferon-free, directly acting antiviral treatment.

1.0 INTRODUCTION

Chronic hepatitis C virus infection is a major public health problem with an estimated 180 million people infected worldwide [1]. In the United States an estimated 4.1 million people are infected and is the principal cause of death from liver disease and leading indication for liver transplantation in the U.S [16-18]. Significant advances have been made with the advent of directly acting antivirals (DAA) against HCV over the last few years.

Liver transplantation for hepatitis C and HIV coinfection has become a controversial indication for liver transplantation because of recently reported poor outcomes. At the same time, the demand for liver transplantation in this challenging cohort of patients has been increasing, as the incidence of HCV has been reported to be between 23-33% in HIV infected people. Natural history studies have demonstrated accelerated rates of hepatic fibrosis as well as complications of cirrhosis as compared to HCV monoinfected people. As a result, liver disease has now become a leading cause of death in HIV-infected subjects.

Survival rates following liver transplantation in HBV/HIV coinfected recipients are excellent and comparable to HBV monoinfected recipients. This is the proof that liver transplantation in the HIV infected recipient is safe and effective providing the coinfection can be controlled in the immunosuppressed HIV-infected recipient. Unfortunately, the 1-year and 3-year survival rates are reported at 76-92% and 72-79% in the HCV monoinfected recipients, compared to 67-88% and 56-62% in HCV/HIV coinfected recipients. The poorer results in the coinfected recipients are related to accelerated recurrence of HCV, and higher incidence of multisystem organ failure in the presence of recurrent HCV. Furthermore, the accelerated pace of HCV recurrence has been exacerbated by a surprisingly high incidence of rejection in the HIV/HCV coinfected recipients, and the requirement for additional immunosuppression to reverse the rejection. Therapy to treat HCV with interferon and ribavirin both pre- and post-transplant has yielded dismal results, with sustained virologic response less than 15%. The overall success in eliminating HCV are poor in HCV monoinfected recipients, but even worse in the HCV/HIV coinfected recipient as a result of overlapping toxicities between ARVs and interferon causing toxicities that require treatment cessation. The use of interferon-based regimens in the post-transplant period is further problematic based on the surprising high rejection rates observed in the HIV infected recipients. Furthermore, use of RBV in HIV/HCV coinfected subjects is associated with an increased incidence of anemia that requires dose reductions, interruptions and treatment with erythropoietin. All these increase the cost and adverse event profile of the therapeutic regimen, which is heightened in pre and post, transplant HIV-infected recipients. Since liver transplantation uses a scarce resource, and results are closely monitored by regulatory agencies, many centers have stopped performing this procedure. Sadly, the cessation of transplanting HIV/HCV coinfected recipients is occurring just as potent DAA therapy is dramatically improving the safety and efficacy of anti-HCV therapy. The ability to safely treat HCV with interferon-free, ribavirin free directly acting antiviral agents with low-potential for drug interactions will be a major clinical feat that will lead to a reduction in the need for liver transplants, improved graft survival and improved overall morbidity and mortality in this challenging patient population.

Recently, several trials have confirmed the efficacy of potent DAA therapy without concomitant IFN in the treatment of HCV. One such drug has been sofosbuvir, an NS5B inhibitor which in combination with IFN-based or IFN free regimens in several trials [7-9] has been to be highly effective. In HCV infected pre transplant subjects, the use of sofosbuvir and ribavirin treatment prior to transplantation

prevented HCV recurrence in the majority of patients who were HCV RNA suppressed at transplant [10]. In subjects who developed recurrent hepatitis C post-transplant, the use of sofosbuvir and ribavirin showed promising early results with over 70% of subjects achieving early sustained virologic response (SVR) [11]. More recently, the use of FDC SOF/LDV with or without ribavirin has been shown to be effective in HCV monoinfected subjects including cirrhotics with SVR rates of at least 95% [12, 13] [14, 15]. The ongoing NIAID SYNERGY trial of the FDC SOF/LDV has shown SVR4 rates of 100% in HCV-monoinfected subjects including cirrhotics [19]. Drug interaction studies have been completed with several HIV antiretrovirals and treatment trials of SOF/LDV in HIV/HCV coinfected subjects have been initiated. The first of such is the ongoing NIAID ERADICATE study using the FDC of SOF/LDV in HIV/HCV coinfected subjects on or off antiretrovirals. In this study, viral suppression occurred rapidly, no major toxicities or HIV breakthroughs were observed and treatment was safe and well tolerated.

1.1 RATIONALE FOR THE STUDY

In the United States 4.1 million people are infected with hepatitis C virus (HCV) and 1.1 million people are infected with human immunodeficiency virus (HIV)[16]. It is estimated that about one third of HIV-infected individuals are also infected with hepatitis C, likely due to shared risk factors for transmission [20-23]. While morbidity and mortality resulting from HIV infection has dramatically decreased over the past three decades due to the advent of antiretroviral (ARV) therapy, deaths related to HCV are substantial [24, 25]. HCV treatment in HIV/HCV coinfected individuals is associated with decreased rates of virologic response and is further complicated by drug interactions and high rates of toxicities [26, 27]. In the United States and Western world, hepatitis C is the principal cause of death from liver disease and the leading indication for liver transplantation and, currently, HCV-associated deaths are comparable to HIV-associated deaths [22]. Coinfection leads to accelerated progression of fibrosis and cirrhosis [28-31], increased risk of developing decompensated liver disease and increased risk for hepatocellular carcinoma (see table) [30, 32-34].

Liver transplantation (LT) is the only viable option for patients with advanced HCV-induced cirrhosis and liver failure. Although historically HIV was considered a contraindication for liver transplantation, studies have shown good transplantation outcomes and minimal HIV-related complications in ARV treated patients [35]. Nevertheless, HIV infected patients are not only less likely to receive a LT than non-infected patients, but they are also at a higher risk of death during the waiting period prior to LT [36].

Liver transplantation in HIV/HCV patients results in worse outcomes than in HCV or HIV patients [1-4]. Similarly, survival rates after LT are significantly lower in HIV/HCV patients than HCV patients [1, 2, 5, 6]. While 1- year and 3- year survival rates in HCV monoinfection are reported at 76-92% and 72-79%, rates with HIV and HCV coinfection are reported at 67-88% and 56-62% [1, 6, 35, 37] Recent studies have shown increased levels of graft loss and acute rejection [6, 35] in coinfected subjects. Spontaneous HCV clearance after LT is rare [35] and reinfection with hepatitis C after liver transplantation is nearly universal. Recurrence of HCV disease is often more severe in subjects with coexistent HIV infection [1, 37] Several studies have demonstrated that progression of fibrosis in post LT is significantly faster than the expected natural history of the disease in the normal host [35, 37, 38]. Resultantly, HIV/HCV patients have more fibrosing cholestatic hepatitis, fibrosis, cirrhosis, severe graft fibrosis and acute HCV events than HCV monoinfected patients. HCV recurrence is the leading cause of

death in both groups, but is more frequent in the HIV/HCV group. In this regard, post-transplant hepatitis C is a common problem in the management and survival of HIV/HCV coinfected patients after liver transplantation. [6, 35]

A second transplantation is not a realistic option for most patients, thus, HCV treatment is often initiated after LT to remove the viral antagonist prior to further disease progression or decompensation. In coinfected subjects, the durations of treatment and doses used were lower than in monoinfected subjects, mainly because of drug-drug interactions with the ARVs that subjects are receiving for the treatment of HIV [37] Rates of sustained virologic response to treatment with interferon (IFN) and ribavirin (RBV) after liver transplantation are similar in both groups (All 4), albeit very low (around 14.8%) However, overlapping toxicities between ARVs and interferon can cause toxicities in coinfected subjects that require treatment cessation, ultimately leading to fewer subjects who are able to complete treatment [37]. Graft rejection associated with the use of pro-inflammatory cytokines such as interferon alpha makes post-transplant treatment of hepatitis C less desirable in this patient population Hence, an ideal regimen to treat this patient population will be an interferon-free, directly acting antiviral treatment. Several studies have now demonstrated the efficacy of SOF/LDV in subjects with cirrhosis and SOF/RBV in transplant subjects [10-13]. SOF/LDV (HARVONI) is now approved in the US for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults. Safety and efficacy of SOF/LDV have not been established in subjects with decompensated cirrhosis. Hence, we propose to perform a pilot study using SOF/LDV fixed dose combination for 12 - 24 weeks to treat HIV/HCV coinfected subjects who are awaiting liver transplant or have received a liver transplantation and present with post-transplant hepatitis C. This study will provide a proof of concept to eradicate chronic hepatitis C in this vulnerable population and alter the natural history of post-transplant hepatitis C.

Sofosbuvir: sofosbuvir (formerly PSI-7977) is a nucleotide analog that is a potent and selective inhibitor of NS5B-directed hepatitis C virus (HCV) replicon RNA replication in vitro approved for the treatment of chronic HCV infection.

Please refer to the package insert for additional information on sofosbuvir including [39]:

In Vitro Anti-HCV Activity
Nonclinical Pharmacokinetics and In Vitro Metabolism
Nonclinical Pharmacology and Toxicology
Clinical Experience
Clinical Experience with sofosbuvir
Activity of sofosbuvir against Human Immunodeficiency Virus
Overall sofosbuvir SAE Summary

Ledipasvir (formerly GS-5885)**:** ledipasvir is a novel HCV NS5A inhibitor that has demonstrated potent anti-HCV activity against genotype (1a and 1b) HCV infection.

Please refer to the package insert for additional information on ledipasvir including:

In Vitro Anti-HCV Activity
Nonclinical Pharmacokinetics and In Vitro Metabolism
Nonclinical Pharmacology and Toxicology

Clinical Experience
Summary of Additional Clinical Experience with ledipasvir
The adult safety database for ledipasvir includes data for over 500 healthy volunteers and over 1,000 subjects exposed to at least one dose of ledipasvir in the 6 ongoing Phase 2 studies. Over 700 subjects have been exposed to ≥12 weeks of ledipasvir containing regimens.

Safety Summary: In summary, the safety and PK data support ongoing evaluation of ledipasvir in 2 or 3 drug combination regimens. An unblinded Data Monitoring Committee (DMC), which met 3-4 times/year, monitored the Phase 2 studies listed above. On October 10, 2014 the FDA approved the combination product ledipasvir 90mg/sofosbuvir 400mg called Harvoni.

SOF/LDV Fixed Dose Combination (FDC)

SOF/LDV fixed dose combination (FDC) tablets combine these 2 HCV specific direct acting antiviral (DAA) agents into a single tablet for the treatment of chronic HCV infection.

Please refer to the package insert for additional information on the SOF/LDV FDC including [40]:

In Vitro Anti-Hepatitis C Virus Activity
Nonclinical Pharmacokinetics and In Vitro Metabolism
Nonclinical Pharmacology and Toxicology
Clinical Experience
Summary of Additional Clinical Experience

Rationale for the Current Study Design
The overarching goal of this study is to provide the transplant community with guidance on treatment strategies using sofosbuvir based DAA therapies in patients with HIV-HCV pre and post-liver transplant. The study design includes both a retrospective and a prospective component.

10-20 subjects will be enrolled in the prospective arm designed to evaluate the efficacy and safety of the SOF/LDV FDC tablet, for treatment durations of 12 to 24 weeks, in chronic genotypes 1, 4, 5 & 6 in HIV/HCV coinfected subjects with pre or post liver transplant HCV. Pre-transplant subjects will be treated for 12 - 24 weeks or up to the time of liver transplant (LT). Post-transplant subjects without cirrhosis will be treated for 12 weeks and post-transplant patients with cirrhosis will be treated for 24 weeks.

In addition, the safety and efficacy of sofosbuvir based DAA therapies will be elucidated from retrospective data and contribute to this goal. Very little is known about the long-term benefits of DAA therapy in the transplant candidates and recipient, and the retrospective cohort arm allows longitudinal follow-up of those who have been previously cured with sofosbuvir based DAA therapy to determine rates of reversal of decompensation, reversal of cirrhosis and improvements in graft survival.

There is a significant unmet medical need for IFN-free all oral regimens for the treatment of chronic HCV infection in HIV/HCV coinfection patients, particularly in patients with advanced disease and those with post-transplant hepatitis C given the toxicity and tolerability issues associated with these medications, the unwillingness of many patients to be treated with PegIFN and/or RBV, as well as the

substantial numbers of patients who cannot receive PegIFN and/or RBV due to contraindications [41].One such drug has been sofosbuvir, an NS5B inhibitor which in combination with IFN-based or IFN free regimens in several trials (1-3) has been shown to be highly effective. In HCV infected pretransplant patients, the use of sofosbuvir and ribavirin treatment prior to transplantation prevented HCV recurrence in the majority of patients who were HCV RNA suppressed at transplant (4). In patients who developed recurrent hepatitis C post-transplant, the use of sofosbuvir and ribavirin showed promising early results with over 70% of patients achieving sustained virologic response 4 weeks post treatment (SVR_4). (5) FDC SOF/LDV for 12 weeks with or without ribavirin has been shown to be effective in HCV monoinfected patients with SVR rates of at least 95% [13-15]. Rates of SVR were slightly lower (86-88%) in treatment experienced patients with cirrhosis treated for 12 weeks but SVR increased to 100% with treatment for 24 weeks. The ongoing NIAID SYNERGY trial of the FDC SOF/LDV has shown SVR12 rates of 100% in HCV-monoinfected subjects including cirrhotics (8). Drug interaction studies have been completed with several HIV antiretrovirals and treatment trials of SOF/LDV in HIV/HCV coinfected subjects have been initiated. The first of such is the NIAID ERADICATE study using the FDC of SOF/LDV in HIV/HCV coinfected subjects on or off antiretrovirals. In this study, viral suppression occurred rapidly, no major toxicities or HIV breakthroughs were observed and treatment was safe and well tolerated.

Rationale for Studying HIV/HCV Coinfected Subjects

HIV/HCV coinfected subjects have lower rates of SVR when treated with combination therapy using PegIFN/RBV when compared to HCV monoinfected subjects. HIV/HCV coinfected subjects also have faster rates of progression and a higher likelihood of development of end stage liver disease and decompensated liver failure [26, 42]. DAAs that do not rely on host immune system exclusively to abrogate HCV replication may be an effective approach among HIV/HCV coinfected subjects regardless of race and IL28B genotype.

Furthermore, use of RBV in HIV/HCV coinfected subjects is associated with an increased incidence of anemia that requires dose reductions, interruptions and or treatment with erythropoietin. All these increase the cost and adverse event profile of the therapeutic regimen. The development of a treatment regimen without PegIFN/RBV for genotype 1 patients co-infected with chronic HCV infection and HIV-1 infection would allow for increased access to successful treatment to a significant proportion of the HCV-infected population. Safety, tolerability and efficacy of IFN free regimens appear comparable between the HIV/HCV coinfected and HCV monoinfected subjects supporting the evaluation of similar regimens to those under evaluation in HCV monoinfection. Furthermore, certain studies suggest that patients with a robust immune status respond better to HCV therapy [43].

Overall Risk/Benefit Assessment

The SOF/LDV FDC product combines a potent HCV nucleotide inhibitor and a potent HCV NS5A inhibitor, and has the potential to be a once-daily regimen for the treatment of chronic genotype 1 HCV infection.

The potential benefits of SOF/LDV FDC product for the treatment of chronic HCV are:

- Greater antiviral efficacy (i.e., rapid and durable eradication of HCV) compared to the current standard of care

- A reduction in the AEs currently associated with the use of PegIFN, RBV, and/or available protease inhibitors (telaprevir, boceprevir)
- Shortened duration of therapy
- Increased adherence to therapy with the convenience of a once daily, all oral, FDC

The combination of sofosbuvir 400 mg and ledipasvir 90 mg has been administered in studies to over 2,500 subjects. A review of the safety data from completed studies shows that treatment with sofosbuvir and ledipasvir or FDC has been generally well tolerated. No deaths or discontinuations of study drug due to AEs have been reported. No Grade 4 or clinically relevant Grade 3 laboratory abnormalities have been reported. No trends in vital sign changes have been observed following administration. The favorable safety and efficacy profiles of support further evaluation of this combination.

Postmarketing cases of symptomatic bradycardia, including fatal cardiac arrest and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with SOF/LDV FDC. Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown. Coadministration of amiodarone with SOF/LDV FDC is not recommended.

Rationale for the use of Interferon-free, all Oral Regimen
HIV-infected subjects seem to have lower responses to HCV treatment using interferon based regimens. Since HIV infection is by itself an immunoregulatory disease, it is believed that these subjects will have less optimal responses to immune based therapies. However, use of non-immune based directly acting antiviral therapies that do not rely on host immunity excessively, seem to work very well in HIV infected subjects. For example, HIV infected subjects respond to antiretroviral therapy regardless of baseline CD4 T cell counts. Hence, it is expected that HIV-infected subjects would have better rates of SVR when treated with non-immune based, directly acting agents for HCV. Second, we have previously demonstrated that HIV-infected subjects who control HIV replication by themselves without the aid of ART seem to have faster clearance than those subjects with similar CD4 T cell counts, but requiring ART to suppress HIV replication [28]. Third, we are using an extended treatment duration for these subjects (12 to 24 weeks). We believe this would allow us to maximize the rates of SVR for HIV infected pre and post liver transplant subjects in which relapse can be severe and associated with significant worsening of decompensation.[44]

2.0 OBJECTIVES

2.1 Primary Objectives

1. To assess the safety, tolerability, and efficacy of sofosbuvir based DAA therapy for 12 – 24 weeks in HIV/HCV coinfected participants pre- and post-liver transplant.

2. To assess the safety, tolerability, and efficacy of a fixed dose combination (FDC) of sofosbuvir and ledipasvir (SOF/LDV) for 12 to 24 weeks in HIV/HCV coinfected participants pre or post liver transplant.

2.2 Secondary Objectives

1. To evaluate changes in HCV viral kinetics with SOF/LDV or sofosbuvir based DAA therapies in HIV/HCV coinfected subjects with pre or post liver transplant HCV

2. To evaluate the proportion of subjects with HCV viral loads below the level of quantification at various time points of the study

3. To determine sustained virologic response rates with FDC SOF/LDV or sofosbuvir based DAA therapies.

4. To identify the determinants of response to interferon sparing therapy in eradicating HCV in pre or post liver transplant HIV/HCV coinfected subjects

5. To identify the host genetic, protein, gene, and proteomic factors that are associated with responses to interferon (IFN) sparing therapy in in pre or post liver transplant HIV/HCV coinfected subjects (*prospective arm only*)

6. To determine if levels of interferon-stimulated genes (ISG) expression in PBMCs or liver can predict rapid virologic response (RVR), end of treatment response (ETR), and sustained virologic response (SVR) in participants receiving IFN sparing therapy *(prospective arm only)*

7. To evaluate the proportion of subjects whose ALT normalizes during therapy and between baseline and SVR

8. To evaluate the emergence of viral resistance during therapy with FDC SOF/LDV or sofosbuvir based DAA therapies

9. To evaluate change in liver fibrosis and liver function before and after treatment with FDC SOF/LDV or sofosbuvir based DAA therapies.

3.0 STUDY DESCRIPTION

Approximately fifty HIV/HCV coinfected patients with decompensated liver disease will be enrolled in the study. Ten (up to twenty) subjects will be treated with FDC SOF/LDV pre or post liver transplant and followed prospectively. Forty + subjects will be enrolled retrospectively with the intent to capture all patients who have been exposed to sofosbuvir based DAA therapies at participating sites since 1/2014, and to mirror the population being enrolled prospectively.

In addition, participants in the retrospective arm will be contacted to consent to one prospective study visit for liver staging to determine rates of reversal of decompensation, reversal of cirrhosis and improvements in graft survival post treatment, and for future contact by the NIH Clinical Center to assess longer term outcomes when this study ends.

3.1 Retrospective Arm

Participating sites will collect clinical data on all of the HIV/HCV co-infected patients with decompensated liver disease (CPT >7 pre or post liver transplant) treated with sofosbuvir based DAA therapies since 1/2014 at their center. This will be done under IRB approved waiver of consent if possible so that all treated patients meeting the inclusion criteria can be included to avoid statistical bias. Data collected will mirror the data collected in the prospective arm. In addition, participants will be contacted to provide consent to return to the site for one visit for current liver staging to evaluate reversal of fibrosis (unless liver staging by Fibroscan or liver biopsy was done in the previous 12 months), and to be contacted in the future by the NIH Clinical Center for long term follow-up.

- Efficacy will be defined as HCV RNA undetectable ≥ 12 weeks post end of sofosbuvir based DAA therapy.
- Safety and tolerability will be defined by
    - discontinuation rates
    - rates of hospitalization during DAA therapy
    - frequency of anemia requiring blood transfusion or EPO
    - survival.
- Reversal of decompensation: defined by CP score and MELD score at last follow-up (evaluated at time to event given the variability in length of follow-up post treatment)
- Reversal of fibrosis: defined by liver fibrosis by Fibroscan or biopsy at last follow-up (evaluated at time to event given the variability in length of follow-up post treatment)

3.2 Prospective Arm

The cohort of pre-transplant patients with cirrhosis due to hepatitis C will be treated with SOF/LDV until LT or for a maximum of 24 weeks. Patients with and without HCC within Milan criteria are eligible. Another cohort of liver transplant recipients with recurrent HCV infection post liver transplant will also be treated with SOF/LDV for a period of 12 weeks (no cirrhosis) or 24 weeks (cirrhosis). Patients with fibrosing cholestatic hepatitis are eligible and will be treated for 12 weeks.

Starting with Day 0, all subjects will receive SOF/LDV for 12 or up to 24 weeks. The total amount of time required to complete all the study visits is approximately 56 - 68 weeks from the screening period through the end of the follow-up visits:

- Up to 8 weeks Screening period
- 12 or 24 week treatment period
- 12 and 24 week post-treatment follow-up visits (SVR12 and SVR24)
- 36 weeks post-treatment to assess late viral relapse

Subjects identified to have mutations leading to SOF or LDV resistance following sequencing and phenotypic analysis will be requested to return at 12-week intervals for up to 36 weeks to determine the time required for the resistant virus to return to background levels.

3.3 STUDY ENDPOINTS

3.3.1 Primary Endpoints

- Safety and tolerability of SOF/LDV for 12 to 24 weeks
- Proportion of subjects achieving SVR_{12} (HCV RNA <LLOQ 12 weeks after completion of treatment)

3.3.2 Secondary Endpoints

- Correlation of the slope of HCV viral load decline (early viral kinetics) with sustained virologic response at 24 weeks post-treatment (SVR_{24})
- Proportion of subjects achieving SVR_4 and SVR_{24} (HCV RNA < LLOQ at 4 and 24 weeks after completion of treatment)
- RVR_4, (RVR_4: HCV RNA<LLOQ at Week 4): Correlation of early viral kinetics with the percentage of subjects achieving RVR_4.
- End of treatment response (ETR: HCV RNA<LLOQ at end of treatment). Correlation of early viral kinetics to the percentage of subjects who achieve ETR.
- Correlation of early viral kinetics to the percentage of subjects who achieve SVR_{12}.
- Viral relapse: Correlation of early viral kinetics with the percentage of subjects who develop viral relapse.
- Differential interferon sensitive gene (ISR) response to therapy in subjects treated for 12 weeks who do and do not attain RVR_4 and SVR.
- Host genetic and proteomic factors in subjects with differential RVR_4 and SVR HCV quasispecies evaluation at baseline and during therapy to determine emergence of resistance subjects who attain RVR_4, and those who achieve SVR.
- HIV and HCV immunologic (adaptive and innate) correlates of SVR and RVR
- Change in liver fibrosis before and after treatment as determined by standard of care liver staging method.

4 STATISTICAL ANALYSIS

4.1 Sample Size Requirements

The sample size of 50 was chosen for 3 reasons:

1. This is an achievable sample size given the number of known pool of HCV/HIV coinfected liver transplant candidates and recipients at the participating study sites and the available time for recruitment. This sample size will also represent the largest experience with interferon- and ribavirin-free therapy in this specific population. In terms of the primary efficacy endpoint, combined (pre and post-transplant) and separate analyses of SVR_{12} will be estimated. Table 1 shows the width of a 95% exact confidence interval for the probability of SVR_{12} as a function of the number of SVRs in a sample size of 50. For instance, if all 50 subjects have sustained virologic response, we can be 95% confident that the true SVR probability is between 0.929 and 1.

Table 1: SVR_{12} Confidence Interval Table

50	48	46	44	42	40
0.929-1	0.863-0.995	0.808-0.978	0.757-0.955	0.709-0.928	0.663-0.900

Exact 95% confidence interval if the number of SVRs out of 25 is as shown in row 1.

2. A sample size of 50 (pre and post-transplant) is sufficient to address the safety endpoints. If the true event probability is 5% or more, there is about a 92% chance of observing at least one such adverse event (Table 2). Consequently, if no one has a given type of AE, we can be confident that its true probability is under 5%. This trial will provide preliminary evidence on the safety and efficacy of FDC in pre or post liver transplant HIV/HCV coinfected subjects.

Table 2: Adverse Event Probability Table

.01	.05	.10	.15
39%	92%	99.5%	99.97%

For AE probabilities shown in row 1, row 2 gives the probabilities of observing at least 1 participant with the AE among 50 total participants.

3. A sample size of 50 is adequate to support the mechanistic virologic and immunologic studies.

4.1.1 Primary Endpoint

The primary efficacy endpoint is SVR_{12} (HCV RNA <LLOQ 12 weeks after cessation of therapy).

4.1.2 Secondary Endpoints

Secondary efficacy endpoints include: HCV RNA < LLOQ at 4 and 24 weeks after discontinuation of therapy (SVR_4 and SVR_{24}); viral breakthrough; and relapse.

4.1.3 Safety Endpoints

The primary safety endpoint is any AE leading to permanent discontinuation of study drug(s).

4.1.4 Other Endpoints of Interest

Additional efficacy evaluations may include HCV RNA change from Day 0; ALT normalization; and viral kinetic parameters.

4.2 Analysis Populations

Safety and efficacy will be evaluated using the safety population.

4.2.1 Efficacy Population

The primary analysis population for efficacy analysis will be defined as all participants who received at least one dose of study drug.

4.2.2 Safety Population

The primary analysis set for safety analyses will include subjects who received at least one dose of study drug.

On treatment data will be analyzed and defined as data collected from the first dose of study drug through the date of last dose of study drug plus 30 days.

4.3 Data Handling Conventions

Missing data can have an impact upon the interpretation of the trial data. Other than the endpoints discussed below, values for missing data will not be imputed.

For the analysis of post-baseline categorical efficacy endpoints, if a data point is missing and is preceded and followed in time by values that are deemed successes, then the missing data point will be termed a success; otherwise the data point will be termed a failure.

Any subject with missing data due to premature discontinuation of the study medication will be considered a failure at the time points on, or following, the date of discontinuation. If no HCV RNA values are obtained after the last dose of study medication, the subject will be considered a treatment failure for the SVR endpoints.

Where appropriate, safety data for subjects that did not complete the study will be included in summary statistics. For example,

- If a subject received study medication, the subject will be included in a summary of adverse events according to the treatment received; otherwise, if the subject is not dosed then they will be excluded from the summary.

- If safety laboratory results for a subject are missing for any reason at a time point, the subject will be excluded from the calculation of summary statistics for that time point. If the subject is missing a pre-dose value, then the subject will be excluded from the calculation of summary statistics for the pre-dose value and the change from pre-dose values.

Values for missing vital signs data will not be imputed; however, a missing Day 0 result will be replaced with a screening result, if available.

4.4 Efficacy Analyses

4.4.1 Primary Analysis

The primary efficacy endpoint is SVR_{12} (HCV RNA <LLOQ 12 weeks after cessation of therapy.)

There is no active comparator group for this study (as in most clinical trials with all oral therapies in these populations).

In the primary efficacy analysis, an exact Clopper-Pearson 95% confidence interval will be computed for the SVR_{12} rate.

The primary analysis will be performed after all enrolled subjects have been followed through 12 weeks post-treatment or discontinued from study.

4.4.2 Secondary Analysis

The proportion of subjects with HCV RNA below the LLOQ over time (including SVR endpoints) will be presented.

Descriptive summaries and listings will be provided for additional efficacy evaluations of the proportion of subjects who experience virologic failure and other endpoints of interest including ALT normalization, plasma HCV RNA actual values, and change from baseline. Heterogeneity among the study populations (pre- versus post-transplant, severity of liver disease, type of ARVs, baseline characteristics and others) and limited sample size will preclude us from performing extensive multivariate models to determine predictors of treatment success or failure.

Exploratory regression analyses may be performed to assess the relationship between demographic, baseline characteristics, (including baseline viral load, genotype, age, sex, race, ethnicity, presence/absence of cirrhosis, baseline ALT level, prior treatment experience, response to previous treatment [if applicable], and BMI) and antiviral activity (as measured by HCV RNA log reduction).

Details on efficacy analyses will be described in the statistical analysis plan.

4.5 Safety Analysis

Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, and vital signs measurements at various time points during the study, as well as the documentation of AEs.

5 PATIENT POPULATIONS

5.1 Retrospective Arm Inclusion Criteria

The intent of the Retrospective Arm is to capture all HIV/HCV coinfected patients exposed to sofosbuvir based DAA therapy since 2014, to mirror the population enrolled in the Prospective Arm.

<u>Liver transplant candidates (listed) and decompensated cirrhotics (not listed) for liver transplant</u>

1. Treated with sofosbuvir based DAA for any duration since 2014
2. Age >18 years at time of treatment
3. Pre-treatment Child's Pugh score of 7 or greater
4. Pre-treatment laboratory MELD ≥6 and ≤30
5. Survived at least 12 weeks after start of treatment
6. HIV-positive on stable ART for at least 4 weeks pre-treatment
7. Chronic HCV infection with at least one measurement of plasma HCV RNA ≥ 1,000 IU/mL prior to treatment with sofosbuvir based DAA therapy
8. HCV genotype 1, 4, 5 or 6

<u>Liver transplant recipients</u>

1. Treated with sofosbuvir based DAA post liver transplant for any duration since 2014
2. Liver transplant from 2000 to current
3. Age >18 years at time of treatment
4. Treated initiated at least 1 month post-liver transplant
5. Post-LT stage of liver disease documented within the prior year of treatment start date by standard of care methods of liver staging
6. Survived at least 12 weeks after start of treatment

7. HIV-positive on stable ART for at least 4 weeks pre-treatment
8. Chronic HCV infection with at least one measurement of plasma HCV RNA ≥ 1,000 IU/mL prior to treatment with sofosbuvir based DAA therapy
9. Fibrosis staging done within 1 year of start of DAA therapy
10. HCV genotype 1, 4, 5 or 6

5.2 Prospective Arm Inclusion/Exclusion Criteria

Pre-liver transplant candidates

- Enrollment will be targeted to occur at least 12 weeks prior to anticipated transplant date.
- Screening laboratory MELD ≥6 and ≤20 (NIH) or ≤30 (non-NIH sites)

Post-liver transplant recipients

- Recipients with evidence of recurrent HCV viremia
- Subjects with compensated and decompensated liver disease
- Screening laboratory MELD ≥6 and ≤20 (NIH) or ≤30 (non-NIH sites)
- Life expectation of >12 weeks

Inclusion Criteria

1. Over 18 years of age at screening
2. Female participants of child bearing potential must have a negative urine pregnancy test at day 0 prior to dosing.
3. Has received a liver transplant for HCV or has decompensated cirrhosis (Child's Pugh score of 7 or greater)
4. Have HIV-1 infection and either:
   a) On HIV medications (antiretrovirals) for at least 4 weeks WITH
      - An HIV viral load less than the level of detection OR
   b) On no HIV medications for at least 8 weeks WITH:
      - A CD4 count of 500 cells/mm3 or more OR
      - HIV viral load of < 500 copies/mL with a stable CD4 count for at least 3 months
5. Chronic HCV infection as documented by at least one measurement of plasma HCV RNA ≥ 1,000 IU/mL during screening and at least one of the following:

   A positive anti-HCV antibody, HCV RNA, or an HCV genotype test at least 12 months prior to baseline (Day 0) visit together with positive HCV RNA test
6. HCV genotype 1, 4, 5 or 6
7. The use of an anti-HCV positive donor is allowed for participants who have detectable HCV RNA at the time of transplant.
8. The use of an HIV+ donor is allowed if the participant is enrolled in an IRB approved HOPE Act protocol at the transplant site. If the HIV+ donor is also HCV co-infected, then the recipient must have detectable HCV RNA at the time of transplant.
9. Able to effectively communicate with the Investigator and other center personnel.
10. Willing to give written informed consent and comply with the study restrictions and requirements.
11. Willingness to allow stored blood or tissue samples to be used in the future for studying liver

disease and immune function.

12. Willingness to permit HLA typing to be performed.
13. Have a transplant team available for all primary and transplant-related care.
14. If not yet transplanted: expected to be at least 12 weeks prior to transplant in order to complete treatment course.
15. If not yet transplanted: Must have prior standard of care liver staging consistent with F4.
16. If not yet transplanted: For pre-LT patients with HCC, they must meet Milan criteria at time of enrollment to be eligible
17. If post-liver transplant, must be at least 1 month since transplant procedure to begin treatment.
18. If post-liver transplant, liver disease staging must be documented within the prior year by standard of care methods of liver staging

Exclusion Criteria

1. Positive HBsAg or anti-HBc at screening.
2. History of any other clinically active chronic liver disease (e.g., hemochromatosis, autoimmune hepatitis, Wilson's disease, ≥1-antitrypsin deficiency, alcoholic liver disease, and toxin exposures).
3. Treatment with unlicensed herbal/natural remedies suggested to be taken for hepatitis treatment, such as Milk thistle, St. Johns Wort or Cats Claw, within 28 days of start of treatment
4. Treatment with IFN, RBV, telaprevir or boceprevir or any other approved or experimental medication with known anti-HCV activity within 1 month prior to screening date
5. Any prior exposure to an HCV NS5a specific inhibitor
6. A personal history of or first degree relative with a history of Torsade de pointes.
7. Abnormal hematological and biochemical parameters, including:
    a. Hemoglobin < 8g/dL
    b. Estimated GFR, calculated by the CKD-EPI equation, <30 mL/min/ per 1.73 m^2
    c. Sodium <120 mmol/L
8. History of major organ transplantation other than liver or kidney transplantation.
9. Difficulty with blood collection/poor venous access for phlebotomy that would prevent the collection of study required samples
10. Infection requiring systemic antibiotics at the time of screening
11. Active or recent history (≤ 6 months) of drug or alcohol abuse
12. Gastrointestinal disorder or post-operative condition that could interfere with the absorption of the study drug.
13. Donation or loss of more than 400 mL blood within 8 weeks prior to first dose administration.
14. Any medications prohibited (see table 2 in section 8.11) within 28 days prior to Day 0 visit and likely required during study treatment period
15. History of clinically significant drug allergy to nucleoside/nucleotide analogs.

16. History or current evidence of psychiatric illness, endocrine, immunologic disorder, pulmonary, cardiac disease, seizure disorder, cancer or other conditions that in the opinion of the investigator makes the patient unsuitable for the study. Chronic medical conditions, especially if treated with medications (such as hypertension), must be stable at the time of screening. No new therapies should be started within 28 days prior to the study that may confound the assessment of study drug safety.
17. Participation in a clinical study (other than an IRB approved HOPE Act protocol involving the utilization of an HIV+ donor) in which an investigational drug, biologic, or device was received within 12 weeks prior to first dose administration.
18. Pregnant/Breastfeeding women

6 SCHEDULE OF VISITS AND PROCEDURES: RETROSPECTIVE ARM

6.1 Waiver of Consent

In order to capture all eligible candidates in the retrospective arm, data will be captured under an IRB approved waiver of consent if sites obtain IRB approval to do so.

6.2 Consent for liver staging and long term follow-up

If participants can be contacted, they will be asked if they would consent to return for one study visit for current liver staging unless standard of care liver staging by Fibroscan or liver biopsy has been performed within 12 months. Each subject will provide informed consent prior to commencement of any study procedures according to ICH and Code of Federal Regulations (CFR). Each subject will be provided a copy of the signed informed consent form. The consent will also include approval to be contacted in the future by the NIH and/or co-investigators for additional longer term follow-up.

6.3 Time-points

Clinical data from day 0 (start of treatment), week 4, and end of treatment (week 12 or 24 depending on treatment duration) will be recorded in the Redcap database. Data will also be recorded at 3 months post treatment with DAA and again at 6 or more months post treatment with DAA. A complete list of study procedures to be captured is outlined in the Schedule of Events (Section 11)

7 SCHEDULE OF VISITS AND PROCEDURES: PROSPECTIVE ARM

Participants will be seen on each study visit at the enrolling center. A complete list of study procedures to be performed is in the Schedule of Events (Section 11).

7.1 Screening (Visit 1)

Each subject will provide informed consent prior to commencement of any study procedures according to ICH and Code of Federal Regulations (CFR). Each subject will be provided a copy of the signed informed consent form.

After a subject has provided informed consent, screening evaluations will be conducted and the investigator and other study personnel will determine if the subject is eligible for participation in the study. Screening will include a review of the medical history, inclusion/exclusion criteria, concomitant medications, physical examination, and blood tests. Screening tests that have been done as part of other studies or at an outside facility can be used if within the acceptable time frame (applicable lab tests within 56 days before enrollment). Some tests in the schedule of events allow the use of historic data to be used, such as the virology panel, HIV VL, CD4+ T-cell count, and HLA. These have been marked accordingly in the schedule of events.

Screening procedures do not need to be repeated within the 8 week screening window unless clinically indicated.

7.2 Liver Staging (Screening)

All pre-transplant subjects must have prior standard of care liver staging consistent with F4. All post-transplant subjects must have stage of liver disease documented within the prior year by standard of care liver staging methods.

7.3 Physical Examination, including vitals signs

All participants will have a physical visit for the final determination of protocol eligibility. In addition, participants will have a physical examination performed at the following time points: Day 0, week 4, week 12 and (if applicable) week 24 on treatment and at 6 months post treatment visits. A targeted physical exam will be performed on participants as needed for AE evaluation.

7.4 Starting SOF/LDV (Visit 2)

The participant will be started on SOF/LDV on Visit 2 (Day 0). For wait-listed patients, treatment start date should coincide with an anticipate time to transplant of at least 12 weeks (based on MELD score).

Blood will be drawn for standard of care labs and for research (HCV viral loads, drug level, immunologic studies, and for storage). For women with childbearing potential, a urine pregnancy test will be done on Day 0 and must be negative prior to dosing with study agent. The Day 0 procedures are summarized in Schedule of Events (Section 11).

7.5 Adverse event assessment and concomitant medications

At each visit, participants will be asked about their state of health and use of any concomitant medication since screening or the previous study visit. They will also be questioned about AEs and their adherence with study restrictions. In addition, participants will be seen at unscheduled visits for a grade 3 or 4 AE or any unexpected AE (adverse event) or potential toxicity.

7.6 Study Visits during treatment

All participants will be seen on days 0, weeks 4, and week 12 EOT, (or week 24 if treated for 24 wks).

- Weeks 4 (+/- 7 days)
- Week 12 [and 16, 20, 24 if applicable] (+/- 10 days)

Plasma HCV RNA will be obtained on each visit. Subjects who fail to achieve >2 $\log_{10}$ HCV RNA drop at this time (unless >2 log drop would be below LLOQ) will be discontinued from therapy unless a review by the PI/Operations Committee determines otherwise.

7.7 Week 12 or 24 Visit / End of Treatment Visit

Week 12 or 24 will mark the last dose of SOF/LDV to be administered. In addition, if a subject's participation terminates prior to end of treatment, the assessments may be performed at any end-of-treatment visit.

7.7.1 **Liver Staging (End of Treatment)**:

All subjects will have end of treatment liver staging by the same method used to stage at screening.

7.8 Day of Transplant (for Pre-Transplant subjects): Liver Explant Tissue

Subjects who receive treatment pre-transplant and achieve SVR, but who nonetheless progress to liver transplantation, will have a portion of the explanted liver snap frozen or placed in RNA- *later* on the day of transplant. See Laboratory Manual for processing protocol.

7.9 Post treatment follow up visits

After discontinuation of the study drug, subjects will be followed at post-treatment Week 12 and 24. The visit windows are shown below

- Follow up visits (+/- 14 days)
- Post treatment optional liver biopsy -7 days / +30 days (but can be done outside this window at the investigator's or physician designee's discretion).

7.10 Early Termination and Early Treatment Discontinuation

Participants who elect to discontinue study drugs prior to treatment completion for medical or personal reasons will be given the option of being followed up at least every 12 weeks for safety and research labs until the end of the study. The participant should have an end of treatment visit scheduled as soon as possible after all therapy is discontinued. Participants with undetectable HCV RNA at the end of treatment should continue to follow the scheduled SVR visits following the date of their last dose of therapy.

For the prospective arm, participants who have detectable HCV RNA at the end of treatment or who relapse post-treatment will be asked to return for visits to determine the persistence of any HCV populations with treatment-emergent substitutions conferring resistance to sofosbuvir. Samples collected will be used to determine the durability of response or the dynamics of any changes in resistance conferring mutations. The reason for any early termination should be documented.

8 STUDY AGENT/INTERVENTIONS: PROSPECTIVE ARM

8.1 Disposition and Dispensation

Study agents will be distributed via the UCSF Investigational Pharmacy according to standard pharmacy procedures.

All drug products will be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug product should not be stored in a container other than the container in which they are supplied. Consideration will be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions will be followed to avoid direct eye contact or exposure through inhalation when handling study drugs.

8.2 Packaging and Labeling of Study Drugs

Each bottle will be individually labeled with the patient ID number, dosing instructions, recommended storage conditions, the name and address of the manufacturer, Investigational Use

Statement ("Caution: New Drug – Limited by Federal [USA] Law to Investigational Use") and that the agent should be kept out of reach of children.

8.3 Formulation of FDC SOF/LDV

SOF/LDV fixed dose combination (FDC) tablets are orange colored, diamond-shaped, film-coated talets containing 400 mg of sofosbuvir and 90 mg of ledipasvir. The tablets are debossed with "GSI" onone side and "7985" on the other side. The SOF/LDV FDC tablets contain the following inactive inredients: lactose monohydrate, copovidone, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol, FD&C yellow # 6 /sunset yellow FCF aluminum lake.

8.4 Storage And Handling of FDC SOF/LDV

SOF/LDV FDC bottles should be stored at room temperature below 30°C (86°F).

8.5 Dosage and Administration of FDC SOF/LDV

SOF/LDV FDC tablet is to be administered once daily with or without food. Each subject must be given instructions to maintain approximately the same daily dosing interval between study drug doses. For missed dose(s) of study medication, subjects will be instructed to take the missed dose(s) of study medication as soon as possible during the same day. Subjects will be cautioned never to double the next dose with a missed dose of study drug under any circumstances.

8.6 Treatment of Participants

All participants will receive 12 or up to 24 weeks of SOF/LDV. SOF/LDV will be administered as a single pill at dose of 400 mg and 90 mg respectively orally once a day. It can be taken with or without food.

If a participant who starts treatment with study drug prior to transplant receives 4 weeks of treatment or less prior to transplant and has detectable HCV at time of transplant, they are eligible to receive full treatment post-transplant.

If a participant who starts treatment with study drug prior to transplant has received more than 4 weeks of treatment prior to transplant, they are NOT eligible to receive full treatment post-transplant, regardless of HCV RNA level at the time of liver transplantation. Therefore, study treatment is discontinued at the time of transplant.

8.7 Dose Modifications/Toxicities

Maximal suppression of HCV replication is most likely accomplished by sustained delivery of antiviral agents at their current recommended doses. Dose reduction, however, would compromise this goal and predispose to the emergence of drug-resistant viral variants. Hence, no dose reduction will be allowed for SOF/LDV. If SOF/LDVis stopped due to toxicity, it must not be restarted.

If treatment with study drug is interrupted for <= 5 consecutive days for reasons other than drug toxicity (such as discontinuation due to GFR < 30), treatment can be reinitiated and the subject can remain in the trial. However, if treatment is interrupted for > 5 days and/or if study drug is interrupted due to drug toxicity, treatment with study drug should be discontinued.

8.8 Dose Modification for SOF/LDV

SOF/LDV dose modifications will not be permitted. If subject meets safety or virologic criteria for discontinuation, the SOF/LDV will be stopped. If a subject forgets to take the medication at the correct time, it may be taken later in the day; however, no more than a single dose should be taken on any calendar day. The subject should resume the standing dosing schedule on the next day. Any treatment interruption or discontinuation will be recorded including the reason for the interruption or discontinuation.

8.9 Criteria Requiring Discontinuation of SOF/LDV

Subjects will be considered treatment failures and will discontinue SOF/LDV if they meet any of the following criteria while taking study drugs:

- Plasma HCV RNA greater than LLOQ after 2 prior consecutive HCV RNA values less than the LLOQ
- Greater than a 1 $\log_{10}$ increase in plasma HCV RNA from nadir
- Less than a 2 $\log_{10}$ decline in HCV RNA after 4 weeks of treatment

If any of these should occur in a subjects who is currently on study drugs, the subject should return within one week for a confirmatory test. If the confirmatory test also meets the same criteria, the subject will be considered a treatment failure and should be discontinued from therapy. Participants will be referred for other treatment options. The anticipated clinical impact of discontinuation should be discussed in advance if possible, particularly if discontinuation is thought to pose a risk to the overall clinical wellbeing of the subject. Those who are discontinued will continue to follow the general study schedule of assessments unless unwilling to do so, in which case they may be seen at least every 12 weeks for safety and research labs until the end of the study. Subjects will be followed closely for resolution of active laboratory abnormalities or adverse events that are considered related to the study agents prior to starting the revised schedule.

Subjects who meet any of the following laboratory criteria must stop all study medication(s):

- Any Grade 3 or greater rash associated with constitutional symptoms
- Any Grade 4 event assessed as possibly, probably, or definitely related to treatment with SOF or LDV

8.9.1 Treatment Failure Criteria After Stopping SOF/LDV

- Have detectable HCV RNA during the post-treatment period (after having achieved HCV RNA <LLOQ at end of treatment).

8.10 HIV Virologic Rebound Criteria for Subjects on ARVs

Subjects on ARVs who have at least 2 consecutive post-Day-0 visit plasma HIV-1 RNA levels ≥ 1000 copies/mL (at least 2 weeks apart) will be considered to have HIV virologic rebound.

Following an initial HIV-1 RNA result of ≥ 1000 copies/mL, subjects on ARVs will be asked to return to the clinic after 2 weeks for a scheduled or unscheduled blood draw for confirmation of HIV virologic rebound. If HIV virologic rebound is confirmed, the blood samples from this visit will be used for HIV-1 genotype/phenotype testing. If no resistance to the subject's current ARV regimen is detected, the subject may continue on current ARV regimen.

HCV study drug should be continued unless safety events warrant the discontinuation of these study drugs, as outlined in section 9.2 of the protocol.

8.11 Concomitant Medications

Concomitant medications taken within 30 days of screening through 30 days following discontinuation of study treatment need to be recorded in the source documents.

The medications listed in Table 2 are prohibited from 28 days prior to the Day 0 (start of treatment) visit through the end of treatment:

- Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters i.e., P-gp) with study drug(s) may result in pharmacokinetic interactions resulting in increases or decreases in exposure of study drug(s). Examples of representative medications which are prohibited from 28 days prior to Day 0 (start of treatment) through the end of treatment are listed below:

- Medications for disease conditions **excluded** from the protocol are not listed under this Concomitant Medication section and are disallowed in the study.

Note: Since this table is likely to change over time, please review the most current package inserts before prescribing new drugs or modifying doses of concomitant medications.

Table 2: Potentially Significant Drug Interactions: Alteration in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interactions[a]

Concomitant Drug Class: Drug Name	Clinical Comment
Acid Reducing Agents	Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of ledipasvir.
Antacids (e.g., aluminum and magnesium hydroxide)	It is recommended to separate antacid and HARVONI administration by 4 hours.

H2-receptor antagonists[b] (e.g., famotidine)	H2-receptor antagonists may be administered simultaneously with or 12 hours apart from HARVONI at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors[b] (e.g., omeprazole)	Proton-pump inhibitor doses comparable to omeprazole 20 mg or lower can be administered simultaneously with HARVONI under fasted conditions.
Antiarrhythmics : digoxin amiodarone	Coadministration of HARVONI with digoxin may increase the concentration of digoxin. Therapeutic concentration monitoring of digoxin is recommended when coadministered with HARVONI. Coadministration of HARVONI with amiodarone may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with HARVONI is not recommended; if coadministration is required, cardiac monitoring is recommended .
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	Coadministration of HARVONI with carbamazepine, phenytoin, phenobarbital, or oxcarbazepine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended.
Antimycobacterials: rifabutin rifampin[b] rifapentine	Coadministration of HARVONI with rifabutin or rifapentine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended. Coadministration of HARVONI with rifampin, a P-gp inducer, is not recommended
HIV Antiretrovirals	
efavirenz, emtricitabine, tenofovir disoproxil fumarate (DF)	Monitor for tenofovir-associated adverse reactions in patients receiving HARVONI concomitantly with the combination of efavirenz, emtricitabine and tenofovir DF. Refer to VIREAD, TRUVADA, or ATRIPLA prescribing information for recommendations on renal monitoring.
Regimens containing tenofovir DF and a HIV protease inhibitor/ritonavir • atazanavir/ritonavir + emtricitabine/tenofovir DF[b] • darunavir/ritonavir + emtricitabine/tenofovir DF[b] • lopinavir/ritonavir + emtricitabine/tenofovir DF	The safety of increased tenofovir concentrations in the setting of HARVONI and a HIV protease inhibitor/ritonavir has not been established. Consider alternative HCV or antiretroviral therapy to avoid increases in tenofovir exposures. If coadministration is necessary, monitor for tenofovir-associated adverse reactions. Refer to VIREAD or TRUVADA prescribing information for recommendations on renal monitoring.
elvitegravir, cobicistat, emtricitabine, tenofovir DF	The safety of increased tenofovir concentrations in the setting of HARVONI and the combination of elvitegravir, cobicistat, emtricitabine and tenofovir DF has not been established. Coadministration is not recommended.
tipranavir/ritonavir	Coadministration of HARVONI with tipranavir/ritonavir is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended.
HCV Products: Simeprevir[b]	Concentrations of ledipasvir and simeprevir are increased when simeprevir is coadministered with ledipasvir. Coadministration of HARVONI with simeprevir is not recommended.
Herbal Supplements: St. John's wort (Hypericum perforatum)	Coadministration of HARVONI with St. John's wort, a P-gp inducer is not recommended

HMG-CoA Reductase Inhibitors rosuvastatin	Coadministration of HARVONI with rosuvastatin may significantly increase the concentration of rosuvastatin which is associated with increased risk of myopathy, including rhabdomyolysis. Coadministration of HARVONI with rosuvastatin is not recommended.

a.This table is not all inclusive.
b. These interactions have been studied in healthy adults.

9 EVALUATION OF SAFETY

All enrolled subjects who have received SOF/LDV will be evaluated for safety. Safety will be assessed by physical examination, vital signs, hematology, and chemistries. The severity of signs, symptoms, and AEs will be determined by using the 2014 DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, with edits made to allow for clinical center normal values.

9.1 Follow-up of Abnormal Laboratory Test Values

In the event of unexplained abnormal laboratory test values, the tests should be repeated as soon as possible and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded.

9.2 Criteria for Premature Withdrawal and Stopping Rules

Subjects have the right to withdraw from the study at any time for any reason. Subjects who withdraw early or who are terminated from study by the Investigator will not be replaced unless they have received no study drugs. In addition to the criteria for stopping subject treatment described in section 8.9, the Investigator or designee also has the right to withdraw subjects from the study for any of the following:

1. Participant's desire to leave study.
2. Pregnancy or breastfeeding.
3. Participant's non-compliance. If a subject misses 5 or more total study visits or > 3 weeks of study drug, the subject will be removed from the protocol by the study team.
4. Termination of study.
5. Development of a medical condition that in the opinion of the Investigator, it is in the subject's best interest to discontinue study drug even if criteria requiring drug discontinuation have not been met.
6. Request of the primary care provider or Investigator if s/he thinks the study is no longer in the best interest of the subject.
7. Clinical reasons believed life threatening by the physician.

10 ADVERSE EVENT REPORTING AND MONITORING

10.1 Definitions

Adverse Event (AE): Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the research

Adverse Reaction (AR): An adverse event that is caused by a drug.

Suspected Adverse Reaction (SAR): An adverse event for which there is a reasonable possibility that the drug caused the adverse event. 'Reasonable possibility' means that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which implies a high degree of certainty.

Serious Adverse Event (SAE):
A Serious Adverse Event is an AE that results in one or more of the following outcomes:

- death
- a life threatening (i.e., an immediate threat to life) event
- an inpatient hospitalization or prolongation of an existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect
- a medically important event*
- Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but they may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Unexpected Adverse Event: An AE is unexpected if it is not listed in the package insert or is not listed at the specificity or severity that has been observed. It is the responsibility of the Sponsor to make this determination.

Serious and Unexpected Suspected Adverse Reaction (SUSAR): A SUSAR is a Suspected Adverse Reaction that is both Serious and Unexpected.

Unanticipated Problem (UP): Any incident, experience, or outcome that is
1. unexpected in terms of nature, severity, or frequency in relation to
    a. the research risks that are described in the IRB-approved research protocol and informed consent document; package insert or other study documents; and
    b. the characteristics of the subject population being studied; and
2. related or possibly related to participation in the research; and
3. places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. (Per the study sponsor, an adverse event with a serious outcome will be considered increased risk.)

Unanticipated Problem That Is Not An Adverse Event (UPnonAE): An incident, experience or outcome that is not associated with an adverse event which meets the 3 criteria of a UP. Examples include occurrences of breaches of confidentiality, accidental destruction of study records, and unaccounted-for study drug

Protocol Deviation:

Any change, divergence, or departure from the IRB approved study procedures in a research protocol. Protocol deviations are designated as serious or non-serious and further characterized as:

- Those that occur because a member of the research team deviates from the protocol.
- Those that are identified before they occur, but cannot be prevented.
- Those that are discovered after they occur

Serious Protocol Deviation: A deviation that meets the definition of a Serious Adverse Event or compromises the safety, welfare or rights of subjects or others.

Non-compliance: The failure to comply with applicable NIH HRPP policies, IRB requirements, or regulatory requirements for the protection of human subjects. Non-compliance is further characterized as

1. Serious: Non-compliance that:
    a. Increases risks, or causes harm, to participants
    b. Decreases potential benefits to participants
    c. Compromises the integrity of the NIH-HRPP
    d. Invalidates the study data
2. Continuing: Non-compliance that is recurring
3. Minor: Non-compliance that, is neither serious nor continuing.

10.2 Assessing Adverse Events

If a diagnosis is clinically evident, the diagnosis rather than the individual signs and symptoms or lab abnormalities will be recorded as the AE.

All grade 3 or higher AEs occurring from the time treatment starts on Day 0 and through the specified study follow-up period will be documented, recorded, and reported. The Investigator will evaluate all AEs with respect to Seriousness (criteria listed above), Severity (intensity or grade), and Causality (relationship to study agent and relationship to research) according to the following guidelines.

10.3 Severity Grading

Severity of AEs will be graded according to the "Division Of AIDS Table For Grading The Severity Of Adult And Pediatric Adverse Events" (Version 2.0, November, 2014).

Adverse Events not found in the Toxicity Table will be assessed for severity and classified into one of the categories below:

- **Grade 1 (Mild)**: Event requires minimal or no treatment and do not interfere with the participant's daily activities.
- **Grade 2 (Moderate)**: Event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Grade 3 (Severe)**: Event interrupts a subject's usual daily activity or functioning and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- **Grade 4 (Potentially Life threatening)**: Events causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death.
- **Grade 5 (Death)**

10.4 Causality Assessment

Causality (likelihood that the event is related to the study agent) will be assessed from the time study dosing begins until 30 days following the last dose considering the factors listed under the following categories:

Definitely Related
- reasonable temporal relationship
- follows a known response pattern
- clear evidence to suggest a causal relationship
- there is no alternative etiology

Probably Related
- reasonable temporal relationship
- follows a suspected response pattern (based on similar agents)
- no evidence of a more likely alternative etiology

Possibly Related
- reasonable temporal relationship
- little evidence for a more likely alternative etiology

Unlikely Related
- does not have a reasonable temporal relationship

OR
- good evidence for a more likely alternative etiology

Not Related
- does not have a temporal relationship

OR
- definitely due to an alternative etiology

Note: Other factors (e.g., dechallenge, rechallenge) should also be considered for each causality category when appropriate. Causality assessment is based on available information at the time of the assessment of the AE. The Investigator may revise the causality assessment as additional information becomes available.

10.5 Reporting Procedures: Prospective Arm

10.5.1 Adverse Events

Throughout the study, the investigator must record all grade 3 or higher events based on the "Division Of AIDS Table For Grading The Severity Of Adult And Pediatric Adverse Events" (Version 2.0, November 2014), not present at baseline, on the appropriate Adverse Event Form within 5 business days of identification of the event. If an event is present at baseline, is clearly documented, and does not change in severity throughout the study, it does not need to be captured on an Adverse Event Form. However, if the event resolves, or begins to resolve, and then worsens again to a grade 3 or higher, it must be captured on an Adverse Event Form.

Within 5 business days of recognition of an adverse event, the Study Coordinator or site investigator will:

- Complete an Adverse Event Form in the RedCap Database.
- Record information on the adverse event in the participant's medical chart.
- Provide follow-up information when it becomes available

10.5.2 Serious Adverse Events

Deaths and immediately life threatening SAEs must be reported in the Redcap Database within 1 business day after the site becomes aware of the event. All other SAEs must be reported within 3 business days of site awareness.

10.5.3 AE and SAE Recording/Documentation/Follow-up

Adverse events will be collected from the time treatment starts on Day 0 through the end of the study follow-up period. Serious Adverse Events will be collected during the treatment phase plus 30 days.

At each contact with the subject as outlined above, information regarding AEs will be elicited by appropriate questioning and examinations and will be immediately recorded on a source document. Source documents will include: progress notes, laboratory reports, consult notes, phone call summaries, survey tools and data collection tools. Source documents will be reviewed in a timely manner by the research team. The onset date, the end date, the severity of each reportable event, and the Investigator's judgment of the AEs relationship to SOF/LDV will also be recorded.

Adverse events will be followed at a minimum until resolution of the AE or a return to baseline laboratory value. SAEs that occur after the study follow-up period that are reported to and are assessed by the Investigator to be possibly, probably, or definitely related must be reported to the UCSF Project Manager and in the Redcap Database, as described above.

10.5.4 Adverse Events and Serious Adverse Events Exempt from Reporting

Elective hospitalizations or hospital admissions for the purpose of conduct of protocol mandated procedures are not to be reported as an SAE unless hospitalization is prolonged due to complications.

10.6 Reporting Procedures: Retrospective Arm

Adverse event and safety monitoring is not required for the retrospective arm since the retrospective arm only involves data collection and elastography for those who consent. Elastography is ultrasound based and is without adverse events. However, sites will be asked to record data on historical adverse events identified in the medical record for data analysis (hospitalizations during treatment with DAA therapy, anemia requiring transfusion or EPO during treatment with DAA therapy, and death) but the retrospective arm participants are exempt from ongoing safety monitoring.

11 SCHEDULE OF EVENTS

11.1 Schedule of Events Prospective Arm

	Screening	Day 0	Week 4	Week 12*	Week 24*	Day of Transplant	3M post treatment	6 M post treatment
			Month 1	Month 3	Month 6 if treated for 24 weeks	If transplant occurs post treatment with study drug	3 Months post treatment	6 Months or greater post treatment
History and Physical	X	X	X	X	X			X
Vital signs and Weight		X	X	X	X		X	X
Height	X							
Urinalysis		X						
Pregnancy Test: Urine		X[1]						
HBsAg	X							
Anti-HBc	X							
Virology Panel: (Historical only)								
Anti-HIV Ab	X							
Anti-HCV Ab	X							
HCV Genotype	X							
Plasma HCV RNA Levels		X	X	X	X		X	X
CD4+ T-cell count		X[2]		X[2]	X[2]		X[2]	X[2]
HIV-1 RNA (bDNA or PCR)		X[2]		X[2]	X[2]		X[2]	X[2]
Standard of care liver staging	X			X[3]	X			
SERUM CHEMISTRY								
Alanine aminotransferase (ALT)		X	X	X	X		X	X
Albumin		X		X	X			X
Alkaline phosphatase		X	X	X	X		X	X
Aspartate aminotransferase (AST)		X	X	X	X		X	X
Bicarbonate (If on ARV regimen containing tenofovir)		X	X	X	X		X	X
Bilirubin, total, direct		X	X	X	X		X	X
Glucose (repeat during treatment, but only if abnormal at baseline)		X	X	X	X			
Phosphate (If on ARV regimen containing tenofovir)		X	X	X	X		X	X
Potassium (If on ARV regimen containing tenofovir)		X	X	X	X		X	X
Sodium		X	X	X	X		X	X
Serum Creatinine		X	X	X	X		X	X
HEMATOLOGY								
Hemoglobin		X		X	X			
Platelet Count		X		X	X			
White Blood Cell (WBC) Count		X		X	X			
Differential		X		X	X			
Neutrophils		X		X	X			
Lymphocytes		X		X	X			
INR		X		X	X			
RESEARCH								

Limited HCV Viral Kinetics		X	X	X	X			
Liver explant tissue (if achieved SVR)						X[4]		
HLA	X[2]							
Blood draw for immunologic studies		X	X	X	X		X	X
Paxgene DNA (6.5 ml)		X						
Paxgene RNA (2.5 ml)		X	X	X	X		X	
IL28B rs12979860 (run off Paxgene DNA sample)		X						
Blood for storage (8 cc SST serum, 6 cc EDTA)		X	X	X	X		X	X

*Subjects who are terminated early or who have early treatment discontinuation should have an end of treatment visit as soon as possible after therapy is stopped.

[1] Urine pregnancy test for females with childbearing potential must be negative on Day 0 prior to dosing with study agent

[2] documented historic results are acceptable. If not available, not required unless considered standard of care, or may be run on stored samples. For HIV-1 RNA and CD4+ T-cell counts, test results from primary care provider should be obtained per standard of care (every 3 months)

[3]only if treatment stops at week 12. Performed at screening and end of treatment

[4] Liver explant tissue collected and snap frozen or placed in RNA- *later* at the time of transplant, but only if subject achieved SVR pre-transplant.

11.2 Schedule of Events Retrospective Arm (Waiver of Consent)

	Screening	Day 0	Week 4	Week 12*	Week 24*	3M post treatment	6 M post treatment
			Month 1	Month 3	Month 6 if treated for 24 weeks	3 Months post treatment	6 Months or greater post treatment
Record Vital signs and Weight		X	X	X	X	X	X
Record Height	X						
Record Urinalysis		X					
Record Virology Panel: (Historical only)							
HBsAg	X						
Anti-HIV Ab	X						
Anti-HCV Ab	X						
HCV Genotype	X						
Record Plasma HCV RNA Levels		X	X	X	X	X	X
Record CD4+ T-cell count		X		X	X	X	X
Record HIV-1 RNA (bDNA or PCR)		X		X	X	X	X
Record Standard of care liver staging	X			X	X		
SERUM CHEMISTRY							
Record Alanine aminotransferase (ALT)		X	X	X	X	X	X
Record Albumin		X		X	X		X
Record Alkaline phosphatase		X	X	X	X	X	X
Record Aspartate aminotransferase (AST)		X	X	X	X	X	X
Record Bicarbonate (If on ARV regimen containing tenofovir)		X	X	X	X	X	X
Record Bilirubin, total, direct		X	X	X	X	X	X
Record Sodium		X	X	X	X	X	X
Record Serum Creatinine		X	X	X	X	X	X
HEMATOLOGY							
Record Hemoglobin		X		X	X		
Record Platelet Count		X		X	X		
Record White Blood Cell (WBC) Count		X		X	X		
Record Differential		X		X	X		
Record Neutrophils		X		X	X		
Record Lymphocytes		X		X	X		
Record INR		X		X	X		

11.3 Schedule of Events Retrospective Arm: One Prospective Visit

RESEARCH	Screening	Day 0
Informed Consent	X	
Return to site for liver staging by Fibroscan. Historical liver staging by Fibroscan or liver biopsy within the previous 12 months for standard of care is acceptable.		X

11.4

12 MECHANISTIC STUDIES: PROSPECTIVE ARM

Viral Kinetics
Samples from Days 0, week 4, and end of treatment (EOT) will be used to assess HCV viral load levels.

HCV Virologic Studies
Full length HCV genome pyro sequencing may be performed using the protocol as described and compared for variability of sequences [45].

rs12979860 (IL28B) Genetic Variant
IL28B genetic variants have been shown to predict HCV treatment induced clearance. The IL28B assay is a real-time PCR assay that utilizes 5-prime nuclease activity of a thermostable polymerase and unique primers and SNP-specific probes to determine the genotype. Test results will not be used as inclusion or exclusion criteria, or to randomize subjects into treatment groups.

Immune Responses to HCV and HIV
Both humoral and cellular immunity against HCV and HIV will be estimated before and during treatment to assess the effect of HCV treatment on host immune response against HCV. We may also perform multiplex PCR assays to detect ISGs before and during treatment.

HCV Genotypic and Phenotypic Resistance Monitoring
Serum samples for genotypic and phenotypic monitoring will be collected

Resistance monitoring will be completed in all subjects who received study drug and were virologic failures as defined.

Subjects who are determined by sequencing and phenotypic analysis to have had mutations leading to SOF resistance will be requested to return at 12 week intervals for up to 48 weeks after the last dose of study drug to determine the time for the resistant virus to return to background levels.

RNA Extraction from liver tissue
In addition, this protocol will also allow for exploration of the potential of an HCV viral reservoir after achieving the primary endpoint of SVR12. Subjects who receive treatment pre-transplant and achieve SVR, but who nonetheless progress to liver transplantation, will have a portion of the explanted liver snap frozen or placed in RNA- *later*. Subsequently, liver RNA will be extracted and an attempt will be made to amplify residual HCV RNA using a protocol adapted from (http://www.ncbi.nlm.nih.gov/pubmed/22729600) that is sensitive to 2 copies of HCV RNA/ug of total liver RNA. If RNA is able to be amplified, the relevant sequences of the HCV genome will be determined as above. The ability to obtain sufficient quantities of liver RNA for this analysis, given that the whole organ is explanted at transplant, is a unique opportunity to explore the possibility of residual HCV RNA after SVR in this cohort.

13 HAZARDS/DISCOMFORTS/RISKS: PROSPECTIVE ARM

13.1 Drugs

The combination of SOF/LDV is well tolerated with minimal adverse events. The safety profile of SOF includes approximately 1600 chronic HCV-infected subjects that have been administered over 12 weeks of SOF in combination with a DAA, PEG-IFN, and/or RBV. No clinical safety issues related to SOF have been identified to date. The safety profile of LDV includes over 1000 chronic HCV-infected subjects, of whom over 700 have been administered more than 12 weeks of LDV, which was given in combination with other DAAs, PEG-IFN, and/or RBV. No clinical safety issues related to LDV have been identified to date.

Furthermore, there is no expectation of significant overlapping or new, unexpected toxicities upon administration of SOF/LDV together as an FDC. To date, the SOF/LDV FDC ± RBV has been administered to over 500 HCV infected subjects in ongoing phase 2/3 trials, with over 200 subjects having received SOF/LDV FDC ± RBV for 12 weeks or more.

Risk of bradycardia: People taking beta blockers, or who have an underlying cardiac condition or advanced liver disease, may be at increased risk for bradycardia when taking Harvoni or Sovaldi with amiodarone.

Risk of Reduced Therapeutic Effect of Harvoni Due to P-gp Inducers: Rifampin and St. John's wort are not recommended for use with Harvoni as they may significantly decrease ledipasvir and sofosbuvir plasma concentrations.

Related Products Not Recommended: Harvoni is not recommended for use with other products containing sofosbuvir (Sovaldi).

Adverse Reactions
Most common (≥10%, all grades) adverse reactions were fatigue and headache.

Resistance
An additional possible risk is the development of class resistance to NS5B inhibitors and NS5A inhibitors. Development of such resistance could affect future therapeutic options. However all efforts will be made to manage the development of class specific mutations that could lead to cross resistance to other NS5B and NS5A inhibitors.

13.2 Procedures

13.2.1 Phlebotomy

The primary risks of phlebotomy include occasional bleeding or bruising of the skin at the site of needle puncture, and the sensation of transient lightheadedness or rarely, fainting and infection. The amount of blood drawn will be within the limits allowed for adult subjects by the NIH CC.

14 HUMAN SUBJECT PROTECTIONS

Participants will be fully counseled prior to entry into the study as to the potential risks of the study. Participants who, in the opinion of the study team, do not fully comprehend these potential risks will not be offered participation in the study. Participants will be monitored closely during their participation in the study.

14.1 Gender, Ethnicity, and Race Considerations

Participants will not be excluded based on gender, ethnicity or race.

14.2 Children and Pregnant Women

This study will be limited to adults 18 aged years or older. Insufficient data are available to evaluate the safety and efficacy of SOF/LDV FDC in the pediatric population. No adequate human data are available to establish whether or not SOF/LDV FDC poses a risk to pregnancy outcomes. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with SOF or LDV at exposures greater than those in humans at the recommended human dose. Any woman of child-bearing potential must have a negative urine pregnancy test on the first day of treatment (Visit 2/Day0) prior to receiving the first dose of FDC.

14.3 HIV Testing

Candidates without confirmed HIV infections will have HIV testing at screening. If HIV negative, they will be excluded from enrollment as this study is designed for HIV positive participants.

15 BENEFITS/COMPENSATION/ALTERNATIVES

15.1 Benefits

Participants may have the benefit of suppression or eradication of hepatitis C virus. Study medications will be provided free of charge to all participants.

There may be no benefits to participating in this study.

15.2 Alternatives

Participants can receive approved hepatitis C treatment with all oral interferon-free regimen as provided by their insurance and ordered through their private physician or decide not to be treated at this time.

16 DATA SAFETY AND MONITORING

An internal Operations and Safety Committee will meet monthly via teleconference to review ongoing study progress, to address ongoing operational issues that arise during the conduct of the trial, and to monitor accumulating data affecting subject safety.

Monthly teleconferences: The Operations and Safety Committee will review accrual, adverse event summary reports, HCV viral load measurements and treatment response data, and data quality.

Daily: The Operations and Safety Committee will be notified daily of any unexpected serious adverse events. Upon recognition of any safety concerns, a teleconference may be held with the Operations Committee to discuss the concern.

The Operations Committee will consist of the following personnel:

Study Personnel:

- Peter Stock (PI, UCSF)
- Henry Masur
- Beverly Alston-Smith
- Shyam Kotilil
- Theo Heller
- Marion Peters
- Norah Terrault
- Eleanor Wilson
- Rodney Rogers

16.1 Specific Criteria to Pause Enrollment for Virologic/Therapeutic Failure and for Resistance

16.1.1 Virologic/Therapeutic Failure Criteria to Pause Enrollment

- Criteria 1: 5 of the first 20 participants experience treatment failure while receiving treatment

16.2 If Criteria to Pause Enrollment are Met

If criteria 1 is met, the viral kinetic, pharmacokinetic and resistance data will be reviewed with the study team and sponsor, and a decision will be made as to whether to continue further enrollment.

Participants receiving study drugs at this time will continue receiving treatment and follow-up visits through Week 52.

17 STUDY SITE MONITORING

The study will be conducted in compliance with this protocol, International Conference on Harmonization (ICH) Guideline for Good Clinical Practices (GCP), and any applicable regulatory requirement(s). The investigator (and/or designee) will make study documents (e.g., consent forms, data pulls) and pertinent hospital or clinical records readily available for inspection by the local IRB and monitors under contract to NIAID/DAIDS.

As per ICH-GCP 5.18 and 21 CFR 312.50, “clinical protocols are required to be adequately monitored by the study sponsor.” Monitors under contract to NIAID/will visit the clinical research site to monitor all aspects of the study in accordance with the appropriate regulations and the approved protocol. The

objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent documents and documentation of the ICF process for each monitored subject; 2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs; 3) to compare abstracted information (including CRIMSON data abstracts) with individual participants' records and source documents (participants' charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information); and 4) to help ensure investigators' compliance with the protocol. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit.

A specific protocol monitoring plan will be discussed with the Principal Investigator and study staff prior to enrollment. The plan will outline the frequency of monitoring visits based on such factors as study enrollment, data collection status and regulatory obligations.

18 STORED SAMPLES AND FUTURE RESEARCH: PROSPECTIVE ARM

Extra blood and tissue samples will be stored using a code name that only the study team can link back to the participants. These samples will be stored for future research. Other investigators may want to pursue additional research using these stored samples. If so, the study team will seek IRB approval prior to sharing of any samples. After approval, the study team may send these samples to them, along with the coded label. Investigators will use stored samples only for research. At the completion of the protocol, samples and data will either be destroyed, or after IRB approval, will be transferred to another existing protocol. The IRB will be notified in writing of any loss or destruction of stored samples.

18.1 Research Use of Stored Human Specimens and Data

Samples and data collected under this protocol may be used to study mechanisms involved in the hepatitis C treatment response among participants. Genetic testing will be performed.

Access to research samples will be limited using a locked freezer. Samples and data will be stored using codes assigned by the investigators' designees. Data will be kept in a password-protected computer. Only investigators and their designees will have access to the samples and data. Samples will be stored and tracked utilizing the NCI FCRF Repository operated by Leidos Biomedical Research Inc.

In the future, other investigators (both at NIH and outside) may wish to study these samples and/or data. In that case, IRB approval must be sought prior to any sharing of samples. Any clinical information shared about the sample with or without patient identifiers would similarly require prior IRB approval. The research use of stored, unlinked or unidentified samples may be exempt from the need for prospective IRB review and approval. Exemption requests will be submitted in writing to the NIH Office of Human Subjects Research, which is authorized to determine whether a research activity is exempt.

The NIH Intramural Protocol Deviation definition related loss of or destruction of samples (for example, due to freezer malfunction) will be followed in reporting to the IRB: The deviation compromises the scientific integrity of the data collected for the study.

Any loss or unanticipated destruction of >25% samples (for example, due to freezer malfunction) or data (for example, misplacing a printout of data with identifiers) will be reported to the IRB.

Additionally, participants may decide at any point not to have their samples stored. This will be treated as a withdrawal of the consent and in this case, the principal investigator will request destruction of all known remaining samples and report what was done to both the subject and to the IRB. This decision will affect the subject's participation in this protocol but may not affect participations in any other protocols.

19 DATA MANAGEMENT PLAN

All research data and results will be collected centrally at UCSF using a Redcap data system. The Redcap data will be stored in a professionally managed, secure, web based, collaborative environment which can be made available to co-investigators if needed for analysis and review.

The site Principal Investigator will be responsible for assuring that the clinical data collected is complete, accurate, and recorded in a timely manner. Source documentation (the point of initial recording of information) should support the data collected**,** and must be signed and dated by the person recording and/or reviewing the data. Source documents include all recordings of observations or notations of clinical activities, and all reports and records necessary for the evaluation and reconstruction of the clinical trial. Source documents include, but are not limited to, the subject's medical records, laboratory reports, biopsy reports, progress notes, pharmacy records, and any other similar reports or records of procedures performed during the subject's participation in the study.

All exploratory mechanistic data and stored samples will be recorded and maintained using only the subject's code for identification purposes, and will be maintained by the NIH Intramural investigators.

All research data will be made available to scientific collaborators and supervisors for immediate review, consistent with requirements of confidentiality. All research data, including the primary experimental results, will be retained for a minimum of 5 years to allow for analysis and repetition by others of published material resulting from the data. Data management, including the decision to publish, will be the responsibility of the PI. After publication, all research data that form the basis of that communication will be made available promptly and completely to all responsible scientists seeking further information. Exceptions include those requests that would infringe on confidentiality of clinical data or if unique materials were obtained under agreements that preclude their dissemination.

20 STUDY RECORDS RETENTION

The investigator is responsible for retaining all essential documents listed in the ICH Good Clinical Practice Guideline. All essential documentation for all study subjects is to be maintained by the investigators in a secure storage facility for a minimum of three years per NIAID policies. These

records are also to be maintained in compliance with IRB/EC, state, and federal medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent required by federal, state, and local law.

Should the investigator wish to assign the study records to another party and/or move them to another location, the investigator must provide written notification of such intent to NIAID with the name of the person who will accept responsibility for the transferred records and/or their new location. NIAID must be notified in writing and written NIAID permission must be received by the site prior to destruction or relocation of research records.

21 ANONYMITY AND CONFIDENTIALITY

As each volunteer provides consent and is then enrolled, he or she will be allocated a unique study number. To ensure subject confidentiality, these numeric codes will substitute for personal identifiers on non-clinical research results and stored samples. The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted is prohibited. The results of the research study may be published, but participants' names or identities will not be revealed. Records will remain confidential. To maintain confidentiality, the PI will keep records in locked cabinets and the results of tests will be coded to prevent association with subject names. It is expected that this data will be reported in scientific journals and scientific meetings. Confidentiality of participants will be maintained in all forms of reporting. Participants will be informed in general terms of the results as soon as practical.

22 PROTOCOL REGISTRATION

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) WILL NOT be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

23 CONSENT PROCEDURES

No screening procedures or tests for this study will be done before the consent process is completed. The protocol will be discussed verbally between the participant and one of the investigators or their designee during the screening visit. The participant will be given ample opportunity to discuss any questions. The patient will then be given the consent document to read. After the participant has read this information, there will be further opportunity for discussion with one of the investigators. If protocol enrollment is then agreeable, the participant will sign the standard consent document and be given a copy of the signed document. After the standard consent is signed, screening for study eligibility will commence.

REFERENCES

1. de Vera, M.E., et al., *Survival of liver transplant patients coinfected with HIV and HCV is adversely impacted by recurrent hepatitis C.* Am J Transplant, 2006. **6**(12): p. 2983-93.
2. Duclos-Vallee, J.C., et al., *Survival and recurrence of hepatitis C after liver transplantation in patients coinfected with human immunodeficiency virus and hepatitis C virus.* Hepatology, 2008. **47**(2): p. 407-17.
3. Mindikoglu, A.L., A. Regev, and L.S. Magder, *Impact of human immunodeficiency virus on survival after liver transplantation: analysis of United Network for Organ Sharing database.* Transplantation, 2008. **85**(3): p. 359-68.
4. Vennarecci, G., et al., *Liver transplantation in HIV-positive patients.* Transplant Proc, 2007. **39**(6): p. 1936-8.
5. Terrault, N.A., et al., *Outcomes of liver transplant recipients with hepatitis C and human immunodeficiency virus coinfection.* Liver Transpl, 2012. **18**(6): p. 716-726.
6. Miro, J.M., et al., *Outcome of HCV/HIV-coinfected liver transplant recipients: a prospective and multicenter cohort study.* Am J Transplant, 2012. **12**(7): p. 1866-76.
7. Gane, E.J., et al., *Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C.* N Engl J Med, 2013. **368**(1): p. 34-44.
8. Lawitz, E. and E.J. Gane, *Sofosbuvir for previously untreated chronic hepatitis C infection.* N Engl J Med, 2013. **369**(7): p. 678-9.
9. Osinusi, A., et al., *Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial.* JAMA, 2013. **310**(8): p. 804-11.
10. Curry, M. and e. al, *Pretransplant Sofosbuvir and Ribavirin to Prevent Recurrence of HCV Infection after Liver Transplantation.* Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013; Washington, DC, 2013. **AASLD 2013, abstract LB-2**.
11. Charlton, M. and e. al, *Sofosbuvir and Ribavirin for the Treatment of Established Recurrent Hepatitis C Infection After Liver Transplantation: Preliminary Results of a Prospective, Multicenter Study.* Program and abstracts of the 64th Annual Meeting of the American

Association for the Study of Liver Diseases; November 1-5, 2013; Washington, DC, 2013. **AASLD 2013, abstract LB-2.**
12. Gane, E., C. Stedman, and R. Hyland, *All-oral sofosbuvir-based 12-week regimens for the treatment of chronic HCV infection: the ELECTRON study.* . 48th Annual Meeting of the European Association for the Study of the Liver (EASL 2013). Amsterdam. April 24-28, 2013, 2013. **EASL 2013, Abstract 14**.
13. Lawitz, E. and e. al., *Once daily sofosbuvir/ledipasvir fixed dose combination with or without ribavirin resulted in ≥95% sustained virologic response in patients with HCV genotype 1, including patients with cirrhosis: the LONESTAR trial.* . Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013; Washington, DC, 2013. **AASLD 2013, abstract 215.**
14. Gane, E.J., et al., *Efficacy of Nucleotide Polymerase Inhibitor Sofosbuvir Plus the NS5A Inhibitor Ledipasvir or the NS5B Non-Nucleoside Inhibitor GS-9669 Against HCV Genotype 1 Infection.* Gastroenterology, 2013.
15. Lawitz, E., et al., *Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial.* Lancet, 2014. **383**(9916): p. 515-23.
16. Armstrong, G.L., et al., *The prevalence of hepatitis C virus infection in the United States, 1999 through 2002.* Ann Intern Med, 2006. **144**(10): p. 705-14.
17. Kim, W.R., *The burden of hepatitis C in the United States.* Hepatology, 2002. **36**(5 Suppl 1): p. S30-4.
18. Kim, W.R., et al., *Burden of liver disease in the United States: summary of a workshop.* Hepatology, 2002. **36**(1): p. 227-42.
19. Kohli, A., et al., *Combination oral, ribavirin free, antiviral therapy to optimize treatment outcomes for hepatitis C GT-1 treatment naive patients: interim results from the NIAID SYNERGY Trial.* Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013; Washington, DC, 2013. **AASLD 2013, Abstract LB-8.**
20. Sherman, K.E., et al., *Hepatitis C Virus prevalence among patients infected with Human Immunodeficiency Virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group.* Clin Infect Dis, 2002. **34**(6): p. 831-7.
21. Rosenthal, E., et al., *Liver-related mortality in human-immunodeficiency-virus-infected patients between 1995 and 2003 in the French GERMIVIC Joint Study Group Network (MORTAVIC 2003 Study).* J Viral Hepat, 2007. **14**(3): p. 183-8.
22. Ly, K.N., et al., *The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007.* Ann Intern Med, 2012. **156**(4): p. 271-8.
23. Eyster, M.E., et al., *Natural history of hepatitis C virus infection in multitransfused hemophiliacs: effect of coinfection with human immunodeficiency virus. The Multicenter Hemophilia Cohort Study.* J Acquir Immune Defic Syndr, 1993. **6**(6): p. 602-10.
24. Lesens, O., et al., *Hepatitis C virus is related to progressive liver disease in human immunodeficiency virus-positive hemophiliacs and should be treated as an opportunistic infection.* J Infect Dis, 1999. **179**(5): p. 1254-8.
25. Weber, R., et al., *Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study.* Arch Intern Med, 2006. **166**(15): p. 1632-41.
26. Soriano, V., et al., *Challenges and opportunities for hepatitis C drug development in HIV-HCV coinfected patients.* AIDS, 2011.

27. Sulkowski, M.S., *Hepatitis C Virus Infection in HIV-infected Patients.* Curr Infect Dis Rep, 2001. **3**(5): p. 469-476.
28. Benhamou, Y., et al., *Factors affecting liver fibrosis in human immunodeficiency virus-and hepatitis C virus-coinfected patients: impact of protease inhibitor therapy.* Hepatology, 2001. **34**(2): p. 283-7.
29. Rai, R., et al., *Severity and correlates of liver disease in hepatitis C virus-infected injection drug users.* Hepatology, 2002. **35**(5): p. 1247-55.
30. Thein, H.H., et al., *Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis.* AIDS, 2008. **22**(15): p. 1979-91.
31. Pineda, J.A., et al., *HIV coinfection shortens the survival of patients with hepatitis C virus-related decompensated cirrhosis.* Hepatology, 2005. **41**(4): p. 779-89.
32. Hernandez, M.D. and K.E. Sherman, *HIV/hepatitis C coinfection natural history and disease progression.* Curr Opin HIV AIDS, 2011. **6**(6): p. 478-82.
33. Benhamou, Y., et al., *Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group.* Hepatology, 1999. **30**(4): p. 1054-8.
34. Garcia-Samaniego, J., et al., *Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C.* Am J Gastroenterol, 2001. **96**(1): p. 179-83.
35. Roland, M.E., et al., *HIV-infected liver and kidney transplant recipients: 1- and 3-year outcomes.* Am J Transplant, 2008. **8**(2): p. 355-65.
36. Ragni, M.V., et al., *Pretransplant survival is shorter in HIV-positive than HIV-negative subjects with end-stage liver disease.* Liver Transpl, 2005. **11**(11): p. 1425-30.
37. Duclos-Vallee, J.C., B. Falissard, and D. Samuel, *Liver transplant outcomes in HIV-infected patients: a systematic review and meta-analysis with a synthetic cohort.* AIDS, 2011. **25**(13): p. 1675-6.
38. Viale, P., U. Baccarani, and M. Tavio, *Liver transplant in patients with HIV: infection risk associated with HIV and post-transplant immunosuppression.* Curr Infect Dis Rep, 2008. **10**(1): p. 74-81.
39. Sovaldi [package insert]. Foster City, CA. Gilead; 2017.
40. Harvoni [package insert]. Foster City, CA. Gilead; 2017.
41. Alter, H.J. and T.J. Liang, *Hepatitis C: the end of the beginning and possibly the beginning of the end.* Ann Intern Med, 2012. **156**(4): p. 317-8.
42. Thomas, D.L., *Options for treatment of hepatitis C in HIV-infected persons.* J Hepatol, 2006. **44**(1 Suppl): p. S40-3.
43. Sidique, N., et al., *HIV/HCV-coinfected natural viral suppressors have better virologic responses to PEG-IFN and ribavirin than ARV-treated HIV/HCV patients.* J Acquir Immune Defic Syndr, 2011. **58**(2): p. e38-40.
44. Afdhal, N., et al., *Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection.* N Engl J Med, 2014. **370**(16): p. 1483-93.
45. Liu, Z., et al., *Accurate representation of the hepatitis C virus quasispecies in 5.2-kilobase amplicons.* J Clin Microbiol, 2004. **42**(9): p. 4223-9.