Clinical Study Protocol

A Novel model of Hepatitis C Treatment as Anchor to Prevent HIV, Initiate Opioid Substitution Therapy, and Reduce Risky Behavior (ANCHOR)

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List of Abbreviations

ACE	Adverse Childhood Experiences
AE	Adverse Event/Adverse Experience
CCMD	Critical Care Medicine Department
Co-Infection	Identifier for those with both HIV and hepatitis B or C
DAA	Directly Acting Antiviral
DC PFAP	DC Partnership for AIDS Progress
EMA	Ecological Momentary Assessment
GMA	Geographical Momentary Assessment
HCV	Hepatitis C Infection
HIPS	HIPS, Inc (partner site)
HIPAA	Health Insurance Portability and Accountability Act
GWU	George Washington University
ANCHOR	Study short name
HRPP	Human Research Protection Program
MSM	Men who have sex with men
NIH	National Institutes of Health
PWID	People who inject drugs
IHV	Institute of Human Virology
IRB	Institutional Review Board
MTA	Materials Transfer Agreement
N	Number (typically refers to number of subjects/sample size)
OST	Opiod Substittion Therapy
OUD	Opiod Use Disorder
PI	Principal Investigator
PrEP	Pre Exposure Prophylaxis
PRO	Patient Reported Outcomes
SAE	Serious Adverse Event/Serious Adverse Experience
SEP	Syrigne Exhange Program
SOM	School of Medicine
SUD	Substance Use Disorder
SVR	Sustained Viral Reponse
TDF/FTC	tenofovir/emtricitabine
UP	Unanticipated Problem
UPnonAE	Unanticipated Problem that is not an Adverse Event
RNI	Reportable New Information
UMDTC	University of Maryland Drug Treatment Center (partner site)

Protocol Summary

Full Title:	*A Novel model of Hepatitis C Treatment to Prevent HIV, Initiate Opioid Substitution Therapy, and Reduce Risky Behavior*
Short Title:	*ANCHOR*
Conducted by:	*Institute of Human Virology, University of Maryland*
Principal Investigator:	*Elana Rosenthal, MD*
Sample Size:	N= *200 for on-treatment (phase 1, n = 100; phase 2, n = 100); will enroll up to 400 for screening*
Study Population:	*Adults infected with HCV*
Accrual Period:	48 months (24 months for phase 1 ; 24 months for phase 2)
Study Design:	*This is an open label, non-randomized, observational pilot study to evaluate a model of care for treatment of hepatitis C in people with ongoing injection drug use. Participants will be treated with direct-acting antivirals (DAA) as per standard of care and will concomittantly be offered pre-exposure prophylaxis for HIV prevention and buprenorphine for treatment of opioid use disorder when clinically indicated.*
Study Duration:	*Start Date: September 2016* *End Date: January 2022*
Primary Objective:	*To evaluate the efficacy of DAAs for treatment of hepatitis C in people with ongoing injection drug use.*
Secondary Objectives:	1) Evaluate uptake of PrEP 2) Evaluate adherence to PrEP 3) Evaluate uptake of buprenorphine when clinically indicated (objective restricted to HIPS) 4) Evaluate retention in buprenorphine program (objective restricted to HIPS) 5) Assess change in risk behaviors at baseline, during, and after HCV treatment 6) Evaluate the impact of active IDU vs non-injecting opioid misuse on efficacy of DAAs for the treatment of HCV 7) Evaluate the impact of OST on HCV treatment outcomes
Exploratory Objectives:	1) Rates of HCV reinfection after treatment with DAAs 2) Rates of new HIV infection 3) Immunologic and virologic correlates of protective immunity against reinfection 4) Evaluate adherence to HCV medication 5) Evaluate psychological, social, and behavioral factors related to drug use

6) Evaluate the impact of collocation of OST on HCV treatment outcomes

Précis

Hepatitis C (HCV) is a chronic infection with significant morbidity and mortality. The development of directly acting antivirals (DAA) has dramatically improved the cure rate of HCV treatment. However, despite the availability of effective therapy, the global epidemic of HCV infection continues to be driven by people with ongoing injection drug use (PWID), who are largely excluded from HCV therapy. Several critical barriers exist preventing high-risk patients' entry to care, including (1) lack of engagement in the traditional healthcare system by marginalized patient populations, and (2) insurance restrictions due to concerns regarding treatment adherence and HCV reinfection. Furthermore, ongoing injection drug use places these individuals at high risk of HIV acquisition. However, studies have repeatedly demonstrated that pre-exposure prophylaxis (PrEP) reduces HIV acquisition and opioid substitution therapy with buprenorphine reduces HIV and HCV acquisition in PWID.

As such, we propose a comprehensive model of care to engage individuals with ongoing injection drug use in treatment of HCV, in conjunction with collocated services to prevent HIV acquisition and HCV reinfection, including pre-exposure prophylaxis and opioid substitution therapy. This pilot trial will demonstrate whether a comprehensive model of care can simultaneously treat HCV, and prevent HCV reinfection, HIV acquisition and effectively treat opioid use disorder.

1 Background Information and Scientific Rationale

1.1 Background Information

Hepatitis C virus (HCV) is a serious infection that chronically infects approximately 135 million people worldwide.(1) There is ongoing acute transmission of HCV, especially in young people who inject drugs,(2) and human immunodeficiency virus (HIV) infected men who have sex with men.(3) Chronic infection with HCV can lead to cirrhosis, liver cancer, and death, and is the leading cause of liver transplantation in the United States.(4) HCV is treatable, and the goal of treatment is to achieve a sustained virologic response (SVR), considered to be a functional cure (absence of plasma HCV RNA 12 weeks after completing therapy). Historically, treatment of HCV using interferon-alfa involved significant toxicities and poor rates of SVR, particularly in patients with HIV and/or black race.

The advent of direct-acting antivirals (DAA) has been revolutionary in the advancement of HCV treatment. DAAs have few side effects, short durations of treatment, and high SVR. In addition, they are effective regardless of race, gender, or HIV status, leaving few barriers to treatment. (5, 6) Therefore, in HCV infected individuals, DAAs have the potential to lower mortality, improve quality of life, reduce long-term costs of complications and interrupt the current global HCV epidemic.(7)

Although DAAs have been extremely effective in curing existing HCV infections, there continues to be transmission of HCV. In 2013, there were an estimated 29,718 cases of acute HCV in the U.S. (8). This acute epidemic of HCV is being driven by individuals with high risk practices, including people who inject drugs (PWID) and men who have sex with men (MSM) (9, 10). Many of these individuals lack access to providers and treatment for HCV (11). Therefore, the current barrier to eradicating HCV is implementing accessible treatment programs in high-risk populations in order to effectively cure those who are chronically infected, in order to prevent transmission of disease.

Further, individuals with HCV and high-risk behaviors are often at risk for HIV acquisition. However, multiple evidence based strategies have been demonstrated to decrease acquisition of HIV in PWID.(12) Specifically, pre-exposure prophylaxis (PrEP) with tenofovir/emtricitabine (TDF/FTC) in PWID has been shown to reduce the risk of HIV by 49% in those with regular use of TDF/FTC, and 74% in those with consistent use.(13) Further, utilizing OST with methadone or buprenorphine significantly reduces incidence of HIV and HCV in PWID with opioid use disorder (OUD).(14)

Despite available therapies to treat HCV and prevent HIV, there are multiple barriers to successfully implementing HCV treatment and HIV prevention strategies in these individuals. PWID are a challenging patient population, often with chaotic lifestyles, distrust of the medical system, and poor healthcare literacy.(15) In addition, many system level barriers prevent these patients from receiving healthcare.(16) However, many of these barriers can be ameliorated by embedding comprehensive, patient-centered services at culturally competent sites, and engaging patients on issues which they consider to be a priority. In comparison to specialized OST centers where addiction treatment exists in a separate silo from other medical care, models of comprehensive care where medication-assisted treatment for addiction is integrated and

collocated with chronic medical care have demonstrated improved uptake of and retention in OST, as well as decreased concomitant drug use.(17, 18) These models have demonstrated greater efficacy in treatment of chronic diseases in PWID, such as HIV.(19-22)

In addition, PWID have demonstrated significant desire to obtain HCV treatment. In the era of complicated, toxic, interferon-based therapy, multiple studies demonstrated over 70-80% interest in initiating treatment for HCV.(23-26) When given scenarios of few side effects or greater than 70% SVR, the interest in uptake of HCV treatment was even higher (89% and 93% respectively).(24) Further, a study of HCV treatment with DAA in people with OUD on OST demonstrated equivalent efficacy of and adherence to treatment as compared to people who do not use drugs. Notably, over 50% of these patients had positive urine drug screens at baseline and during the course of treatment.(27) This indicates that in the era of DAAs, which have minimal side effects and greater than 90% efficacy, we may be able to use HCV treatment as an anchor to engage PWID in HIV prevention.

Therefore, we propose a model of comprehensive care, which uses HCV treatment in embedded clinics as an anchor to engage high-risk populations in medical care. As part of this care, we will offer collocated services to prevent HIV (PrEP), as well as reduce the incidence of HIV and HCV reinfection (buprenorphine in people with OUD).

1.2 Institutional Overview

Overview of the DC PFAP Hepatitis Program

In 2008, the National Institutes of Health and the DC Department of Health collaborated to establish the DC Partnership for AIDS Progress (DC PFAP), a partnership for community-based clinical care and research whose aim is to reduce the incidence and prevalence of HIV/AIDS in the District of Columbia. A plan was developed to create a research program to build a sustainable model for urban areas working to reduce the HIV/AIDS crisis. A needs assessment within the area's medical community demonstrated a significant deficit in hepatitis C virus care and treatment. This led to the development of a Hepatitis branch within DC PFAP, rooted in direct subspecialty medical services and clinical research addressing the limitations of standard of care therapy.

The Hepatitis program is currently based at the Institute of Human Virology and operates out of three campuses: (1) clinical partners within Washington DC, (2) National Institutes of Health, Bethesda, MD and (3) University of Maryland Institute of Human Virology, Baltimore, MD. The overarching goals of the programs are to:

- establish improved access to subspecialty care for underinsured patients with HIV
- develop access to HIV and hepatitis related research for residents of DC
- expand integrated care for hepatitis C in the community HIV clinics
- provide national leadership in the development and delivery of effective, safe, convenient therapies, initially focusing on HCV

The clinical aspects of the program are set within partner centers in Washington DC and Baltimore City in addition to the IHV. At HIPS, there is an embedded hepatitis clinic at this previously non-clinical organization providing services for trans people, people who inject drugs, and sex workers.

In Baltimore City, there is an embedded hepatitis clinic at the University of Maryland Drug Treatment Center (UMDTC). Patients are managed by state of the art standard of care as well as offered opportunities to participate in clinical research as appropriate. To date, over 1240 HIV and HCV infected patients have been linked to care and over 900 patients cured of hepatitis C through treatment with novel directly acting therapy within these subspecialty clinics. Through direct linkage to care, effective treatment, and continual outcome measurement, the Hepatitis program has developed an effective model for management of hepatitis C in an urban setting.

1.3 Treatment

Until recently, a major limiting factor in expansion of treatment for HCV has been standard of care therapy with pegylated interferon, ribavirin, and more recently for genotype 1 disease, boceprevir and telaprevir. These medications have significant side effect profiles, response-based dosing regimens of over 6 months, and decreased efficacy in key groups including: those with genotype 1 disease, HIV coinfection, and cirrhosis. However, there has been dramatic improvement using all oral DAA regimens with sustained virologic response (SVR) rates over 90%, short-duration therapies and well-tolerated, simple regimens including among those with HIV coinfection. However, most data on the use of DAAs is from clinical trials, which often enroll a patient population not representative of the HCV epidemic. Therefore, few studies have been published addressing the efficacy of interferon-free, DAA-based HCV treatment among PWID. However, a study of patients on opioid substitution therapy who were treated with DAAs demonstrated equivalent efficacy and adherence, even amongst those with persistently positive urine drug screens(28), indicating that effective treatment of PWID with ongoing drug use may be feasible.

1.4 Rationale

HIV and HCV are diseases of concern in the Baltimore and DC metropolitan areas. New DAA treatments allow for effective treatment of chronic HCV, however, individuals with high-risk practices are largely excluded from care due to insurance restrictions, and as such, ongoing transmission of HCV persists. This study will demonstrate f*easibility and efficacy of treating people with chronic HCV infection and ongoing injection drug use at clinics embedded in non-traditional healthcare settings.* Further, we aim **to demonstrate a model of care which combines HCV treatment with HIV prevention strategies, in an attempt to cure HCV and prevent incident HIV infection**.

2 Study Objectives

2.1 Primary Objective

Efficacy of DAA for treatment of HCV in people with ongoing injection drug use.

2.2 Secondary Objective

1. Evaluate uptake of PrEP
2. Evaluate adherence to PrEP
3. Evaluate uptake of buprenorphine when clinically indicated (HIPS site only)
4. Evaluate retention in buprenorphine programs (HIPS site only)
5. Assess change in risk behaviors at baseline, during, and after HCV treatment

6. Evaluate the impact of active IDU vs non-injecting opioid misuse on efficacy of DAAs for the treatment of HCV
7. Evaluate the impact of OST on HCV treatment outcomes

2.3 Exploratory Objective

1. Rate of HCV reinfection after treatment with DAAs
2. Rates of new HIV infection
3. Immunologic and virologic studies
4. Evaluate adherence to HCV medications
5. Evaluate the psychological, social, and behavioral factors related to drug use
6. Evaluate the impact of collocation of OST on HCV treatment outcomes

3 Study Design

3.1 Description of the Study Design

This is an open label, observational pilot study to evaluate a model of care for treatment of HCV in people with ongoing injection drug use through embedded clinics at HIPS in Washington, DC (Phase 1 and 2) and the UMDTC in Baltimore (Phase 2), and the IHV while offering collocated HIV preventive interventions when clinically indicated.

3.2 Study drugs

3.2.1 HCV:

For the treatment of chronic HCV, patients will be treated with FDA approved direct-acting antivirals with or without ribavirin as per standard of care per the AASLD/IDSA HCV Treatment Guidelines and per the discretion of the investigator.

3.2.2 PrEP:

For the purposes of pre-exposure prophylaxis for HIV prevention, participants will be offered treatment with tenofovir-emtricitabine (TDF/FTC), as per standard of care per the CDC guidelines and per the discretion of the investigator.

3.2.3 Opioid substitution therapy:

For the treatment of opioid use disorder, eligible participants will be offered treatment with buprenorphine or buprenorphine/naloxone as per standard of care. Buprenorphine will be prescribed by a physician who has completed the buprenorphine waiver training and has DEA approval for prescription of buprenorphine for this indication.

3.3 Research Strategy

Study participants will be selected based on inclusion criteria, and will be treated at the IHV or the HCV clinics embedded at either of 2 sites:

1) The University of Maryland Drug Treatment Center (UMDTC), Baltimore, MD:
    a. A clinic for treatment of individuals with substance use disorder. Participants have access to treatment with methadone, buprenorphine, naltrexone, as well as counseling and primary medical home services.
2) HIPS, Washington, DC
    a. An organization providing services to people who inject drugs, trans persons, and sex workers. Participants have access to HIV and HCV testing, syringe exchange, naloxone distribution, counseling services, case management, community health worker services, as well as drop-in center with on-site laundry, shower, internet and community lunch.

All participants will be treated for chronic HCV with DAAs as per standard of care (see 3.2.1). All eligible participants will be offered PrEP with TDF/FTC per CDC guidelines (see 3.2.2) and treated in conjunction with HCV care. Eligible individuals at the HIPS site with opioid use disorder will be offered buprenorphine (see 3.2.3) in conjunction with HCV care.

3.4 Primary Hypothesis

The primary hypothesis is that a comprehensive model of care for individuals with high-risk sexual and drug use practices that incorporates standard of care HCV treatment with collocated PrEP and buprenorphine (when indicated) will result in high rates of HCV cure, as well as decreased incidence of HIV and HCV reinfection.

4 Study Population

Participants are individuals with chronic HCV infection and in the first phase (first 100 enrolled participants) ongoing injection drug use, defined as self-report of injection of a non-prescription drug within three months of screening visit, or in the second phase (enrolled participants 101-200) patients with self-report of opioid misuse within one year.

4.1 Rationale for Subject Selection

Subjects of any gender will be considered for inclusion in this study. There will be no racial, ethnic, or gender discrimination. Persons in jail or prison are not eligible for this study (see 4.3.2). Pregnant and breastfeeding women will not be eligible (see section 4.3.1).

4.2 Subject Inclusion Criteria

To be eligible for participation on this protocol, a participant must satisfy all of the following conditions:

1. Age ≥18 years old
2. Able and willing to sign informed consent
3. Chronically infected with HCV, defined as any individual with documentation of positive HCV antibody and positive HCV RNA test (HCV RNA of 2,000 IU/mL or greater).
4. Willing to have samples stored for future use
5. Ongoing opioid misuse: defined as self-report of either:
    a. Phase 1 (first 100 enrolled participants) Injection of non-prescription opioids within three months of screening visit;
    or
    b. Phase 2 (enrolled participants 101-200) Use of non-prescription opioids within twelve months of screening visit

4.3 Subject Exclusion Criteria

A participant will be ineligible to participate in this study if any of the following criteria are met:

1. Decompensated liver disease (Childs Pugh B or C)
2. Unable to comply with research study visits
3. Poor venous access not allowing screening laboratory collection
4. Have any condition that the investigator considers a contraindication to study participation
5. Pregnant or breastfeeding woman

4.3.1 Justification for Exclusion

Pregnancy: Pregnant women are excluded from this study per FDA guidance, as there are no studies of DAAs in pregnant women, and no DAA is currently FDA approved for use in pregnant women.

Breastfeeding: Breastfeeding women are excluded from this study per FDA guidance as there are no studies of DAAs in lactating women, and no DAA is currently FDA approved for use in lactating women.

Exclusion of Children: Safety and effectiveness of DAAs have not been established in pediatric patients, and as such subjects 18 years of age or younger will be excluded from the study. Because insufficient data regarding dosing or adverse events (AEs) are available in adults to judge the potential risk in children, this study poses greater than minimal risk and does not meet the Department of Health and Human Services guideline 45 Code of Federal Regulations (CFR) 46, subpart D, governing the participation of children in research.

4.4 Vulnerable/Incarcerated Participants

Because of the high rates of incarceration amongst people who use drugs, it is possible that participants will become incarcerated during the course of the study. While we will not enroll participants during a time of incarceration, participants will not be removed from the study if the

study team becomes aware of their incarceration during the study period. This will enable the study team to continue to provide direct acting antiviral medication to the participants, which would not be possible if the participant is removed from the study. In this way, ongoing inclusion in the study will benefit the participant, even during this vulnerable time. Participants will have the right to refuse treatment during incarceration.

Participants who become incarcerated during the course of the study will not have study data collected during their incarceration. In the cases where the study team is made aware of a participant's incarceration while they are on active HCV treatment (taking direct acting antiviral therapy at the time of incarceration), the study team will make a reasonable effort to deliver the remaining course of HCV treatment to the jail/prison so the participant can have the best chance of being cured for hepatitis C and does not develop resistance to hepatitis C medication.

5 INTERVENTIONS

5.1 Assessment of Subject Adherence

Adherence will be assessed by subject interview and pill count as per study schedule.

5.2 Concomitant Medications and Procedures

All concomitant prescription and over the counter medications taken during study participation will be recorded. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician.

5.3 Prohibited Medications

Contraindicated medications will be determined per the package inserts of prescribed medications as per standard of care.

6 Study Schedule

Study visits, including screening, will occur at the IHV and clinics in UMDTC and HIPS based upon scheduling availability to accommodate each treatment group. The research coordinators will also oversee research operations in the clinics. See Appendix B.

All phlebotomy related to the study will be done by a phlebotomist working in the clinic or clinic staff. All laboratory studies related to standard of care will be performed as per the standard practice at the site. All blood samples for storage for research will be couriered to the IHV lab.

Participants will be given a calendar of scheduled study visits and will be informed that any clinic visits outside of scheduled study visits may be either unscheduled visits or non-study visits. Subjects will receive this information when given the visit calendar.

Participants who are no-show for visits will be contacted as per the standard procedure for missed visits at each clinic site.

6.1 Screening /Enrollment

Screening will occur at the collocated HCV clinics at the following sites:

- UMDTC (Phase 2)
- HIPS (Phase 1 & 2)

Subjects who meet inclusion criteria and who consent to the study will be enrolled. Outside labs performed within the last 6 months may be used to determine eligibility.

6.2 Standard of care HCV treatment

All participants will be started on HCV treatment after confirming eligibility on Day 0. Patients will complete visits and laboratory monitoring as per standard of care guidelines.

6.3 Study procedures – HCV treatment

During HCV treatment and in the follow-up period, patients will undergo monitoring for treatment adherence, and complete interval surveys for risk assessement, urine drug screens, HIV antibody/antigen testings, and HCV RNA levels. Blood samples for storage and research may be obtained (PBMC, plasma, serum and Paxgene RNA). Patients may undergo serial evaluation of liver fibrosis with fibroscan. See Appendix A Study Schedule.

6.3.1 Adherence monitoring

On weeks 4, 8, 12 participants will meet with study staff to complete counts of remaining pills, as well as answering questions regarding HCV treatment adherence.

6.3.2 Risk assessments

At screening patients will complete a baseline epidemiologic survey (Appendix C). Patients will also complete interval risk assessments with the HIV Risk-taking Behavior Scale (Appendix D) at weeks 4, 12, 24, 48, 72 and 96. Assessments will be administed by study staff at the time of study visit. As part of standard practice at the HIPS site, patients will be asked about their use of the syringe exchange program (SEP) at those visits. AUDIT-C brief alcohol screen will be administered at the time of fibroscan at weeks 24, 48 and 96 (Appendix E). Additionallly at screening, week 12, and week 24 the validated 16-item HCV-PRO questionnaire will be administed (Appendix F). This version of the HCV-PRO questionnaire was developed to be self-administered for persons with a diagnosis of chronic hepatitis viral infection, including treatment naïve, currently treated, and previously treated but who have remained infected in an attempt to assess change in patient reported outcomes prior to treatment, during treatment, and after treatment completion. At week 24 or next possible time point, participants will be administered the validated Adverse Childhood Experience (ACE) Questionnaire (Appendix H) which has shown to be a significant risk factor for substance use disorders and will better inform our understanding of the study population.

6.3.3 Urine drug screen

Urine will be collected for drug screen at screening, weeks 4, 12, 24, 48, 72, and 96.

6.3.4 Stored sample collection

Blood samples for storage and research will be obtained at screening, total of 11 tsp, and a total of 9 tsp at weeks 4, 12, 24, 48 and 96. Samples collected will include:

- Serum storage (10 mL) SST/tiger top (2 teaspoons)
- Plasma storage (6ml) EDTA (1 teaspoon)
- DNA paxgene will be collected (8.5ml) one time at baseline (1 ½ teaspoon)
- RNA paxgene will be collected (2.5ml) (1/2 teaspoon)
- Peripheral blood mononuclear cells (30 ml) Green top/heparin (6 teaspoons)

6.3.5 Fibroscan

Patients may have assessment of liver fibrosis by transient elastography with fibroscan at screening, 24, 48 weeks, and 96 weeks.

6.3.6 HIV and HCV monitoring

HIV antibody/antigen will be checked at weeks 4, 24, 36, 48, 72, and 96 with a one month window. HCV RNA will be checked per standard of care, and subsequently at weeks 36, 48, 72, and 96 with a one month window.

6.3.7 Viral sequencing

Individuals with new seroconversion to HIV will have sample sent for viral sequencing and phylogenetic analysis. Individuals with detectable HCV RNA after completion of HCV treatment or new infection during the follow up period will have current sample, and baseline stored sample sent for viral sequencing and phylogenetic analysis. Phylogenetic analysis will enable us to demonstrate mode of transmission of new infections and resistance associated variants that may impact ART and DAA therapy in the future.

6.4 Optional Standard of Care PrEP with TDF/FTC

All eligible subjects will be offered initiation of standard of care treatment with TDF/FTC for HIV prevention from Day 0 through week 24 of HCV treatment. Patients will be seen and monitored as per standard of care. Patients who uptake PrEP will be treated for a 12 month time period, and then transitioned to a community provider. The first day of PrEP treatment will be considered day P0. See Appendix A Study Schedule.

On or after week 48, all participants enrolled in ANCHOR study will be administered a brief PrEP Retrospective questionnaire (Appendix K) to clarify why they did or did not uptake PrEP.

6.4.1 Study Labwork

Any participant who seroconverts to HIV while on PrEP treatment will have serum sample collected for sequencing and phylogenetic analysis.

6.4.2 Adherence Monitoring

On weeks P4, P12, P24, P36, and P48 participants will meet with study staff to complete counts of remaining pills, answer questions regarding PrEP treatment adherence, and provide blood samples to evaluate tenofovir levels. Tenofovir levels will be done on the first 50 participants at Month 1, Month 6 and Month 9 treatment.

6.4.3 Linkage to care

Participants will be treated for up to 12 months from the time of initiation of PrEP. As this is a chronic medication, at the end of treatment, patients interested in continuing on PrEP will be linked to care with a community provider.

Any participant who seroconverts to HIV will be immediately linked to care, in DC through the Red Carpet Entry Program, and in Baltimore through the JACQUES program.

6.5 Optional Standard of Care Opioid Substitution Therapy with Buprenorphine

All subjects who meet criteria for opioid use disorder per the DSM-V will be offered initiation of standard of care treatment with buprenorphine for treatment of opioid use disorder. Patients will be seen and monitored as per standard of care. Patients will be offered uptake from day 0 until week 24 of HCV treatment , and will be treated for a 12 month time period, and then transitioned to a community provider. The first day of buprenorphine treatment will be considered day B0. See Appendix A Study Schedule.

6.5.1 Retention Monitoring

Patients will be monitored for ongoing retention in buprenorphine program by observation of buprenorphine prescription. Documentation of buprenorphine prescription will be done at day B0 and weeks B2, B4, B8, B12, B24, B36.

6.5.2 Linkage to care

Participants will be treated for up to 12 months from the time of initiation of buprenorphine. As this is a chronic medication, at the end of treatment, patients interested in continuing on buprenorphine will be linked to care with a community provider.

6.6 Optional Geographic Momentary Assessment

All enrolled subjects in Phase 2 (participants 101-200) will be offered participation in the Geographic Momentary Assesment (GMA), an optional, exploratory outcome through a research collaboration with the National Institute of Drug Abuse (NIDA) to further explore drug use, overdose, risky behaviors, and barriers to hepatitis C treatment and PrEP.

While many patients inducted and stabilized on buprenorphine or methadone reduce or eliminate opioid use, there remains a group of individuals who continue to use opioids despite opioid agonist therapy. Additionally, there are patients in treatment who continue to use drugs other than opioids including alcohol, marijuana, stimulants among others. These individuals remain at

risk for harm including overdose, acquiring or transmitting HIV, HCV, and other diseases, and poor adherence to medical treatment.

This NIDA-developed technology, GMA, combines Ecological Momentary Assessment (EMA), the collection of real-time in the field data via smartphones, with GPS of self-reported data on craving, drug use, and stressors collected daily in real time via a cell-phone based application (APPENDIX G). Using the smartphone's GPS log, we will collect data on participants' locations throughout the day to assess how changes in environment affect mood and activities. GMA overcomes the limitations of retrospective assessments, which may not adequately measure the dynamics of craving or accurately depict the relationships between craving and use (Tiffany & Wray, 2012; Kavanagh et al., 2013; Serre et al., 2015). The GPS receiver chipsets have become ubiquitous in smartphones and, by combining GPS information with information on the strength of signals obtained from cellular data networks and wireless internet data connections (i.e., assisted GPS), smartphones can provide accurate location information more quickly than standalone GPS units and in cases where GPS signals are attenuated (e.g., indoors, in urban areas with many tall buildings) (Zandbergen, 2009; Zandbergen & Barbeau, 2011).

These assessments will be evaluated on an ongoing basis by Drs. Preston and Phillips (sub-investigators on the protocol), who are nationally recognized experts in the field of GMA as it relates to substance use-disorder and drug craving. NIDA has been conducting GMA studies since 2005 and has collected data on over 850 study participants. The results of their work have been published in high-quality journals; the first paper was published in 2009 in Archives of General Psychiatry [30-57]. Recently NIDA used GMA to study the effects of clonidine on relapse to opioid use in patients receiving buprenorphine maintenance which was published in the American Journal of Psychiatry[42].

This exploratory outcome will parallel hepatitis C treatment and PrEP and buprenorphine/methadone treatment as indicated, without impacting the above listed research assessments or study visit schedule. Using cell phones with active data plans provided free to enrolled subjects for one year, subjects will be queried by an GMA-specific application four times per day from Day 0 – Week 24 and one-time daily from Week 25-48 to complete an assessment of drug use, craving, stress, and other social and behavioral factors as an in-depth risk assessment (see Appendix G). Subjects will have training on use of the GMA application on Day 0, and phones will be distributed. Subjects will then complete surveys on a daily basis and will return their cell phones at Week 48. These prompts will take between 5 and 8 minutes on average to complete, and will be associated with weekly remuneration if completed regularly (see section 11). Participants can briefly turn off the alerts if they are driving, showering, etc. Participants are otherwise instructed to respond, even if at work.

For participants enrolled in GMA, at their ANCHOR visits they will complete an Adherence Packet-4 at baseline. The Adherence packet-4 (APPENDIX I) consists of 4 questionnaires (total about 15 minutes) including:

1. **The Perceived Stress scale (PSS)** (Cohen et al., 1983) is a 14-item measure of self-rated stress levels and coping ability over the past month. Takes about 5 minutes (Appendix 37).

2. **HIV Knowledge Questionnaire** (Carey & Schroder, 2002). The HIV Knowledge Questionnaire is an 18-item questionnaire used to assess knowledge of HIV transmission and protective behaviors. The HIV Knowledge Questionnaire shows good internal consistencies (Cronbach's α=.75-.89) and reliability (r=.76-.94). It takes about 3 minutes to complete.
3. **HIV Attitudes Scale.** The HIV Attitudes Scale is an 11-item questionnaire assessing attitudes and concerns about transmitting/contracting HIV. The questionnaire takes about 3 minutes to complete.
4. **Food, Housing, and Health Security Questionnaire (FHHSQ).** This is a condensed 8-item questionnaire including 3 questions from the **NHANES Food-Security Questionnaire** (NHANES FSQ), 4 questions from the **Housing-Security Questionnaire**, and 1 question from the **NHANES HIQ/HUQ**. It takes about 2 minutes to complete.

An Adherence Packet-2 (comprised of questionnaires 1-PSS, and 2-FHHSQ listed above) will be completed at weeks 4, 12, 24, and 48.

6.7 Early Termination Visit

Participants who discontinue HCV treatment prior to treatment completion for medical or personal reasons will be given the option of being followed as per study schedule for risk assessments, lab monitoring, and ongoing optional PrEP and buprenorphine (if already initiated). Participants who discontinue PrEP or buprenorphine will continue to be monitored per the HCV study schedule, however will no longer have monitoring specific to PrEP or buprenorphine. The participant should have an end of treatment visit scheduled as soon as possible after all therapy is discontinued. The reason for any early termination will be documented.

7 Potential Risks and Benefits

7.1 Potential Risks

Given this investigation is centered on implementation of a novel model of care, the main risks are related to any blood draw outside of standard of care, and loss of confidential data.

The potential risks include risks of phlebotomy that include: pain, bruising, fainting and very rarely, infection. These risks will be minimized by having trained staff perform the procedure.

There is potential for loss of confidentiality, which will be minimized by providing privacy during study visits. In addition, all laboratory specimens, and research records will be coded by a number to maintain subject confidentiality. All paper records will be kept locked with limited access. Electronic data will be password protected and will not include participant names or contact details.

Risks from smartphones and GMA. Carrying and using the smartphone could be annoying or embarrassing to the study participant. The smartphone will be collecting personal

information and location, but this information will not be displayed on the phone and not linked to any of personal information/identifiers. A PIN code is needed to access the smartphone and the specific application that is used to provide data. Responses will regularly be transferred from the smartphone to secure password-protected computers located at the National Institute on Drug Abuse (NIDA), limiting the amount of information that is contained on the phone. The data does not contain information that could be used to identify participants. The data is transferred from phone to NIDA secure server.

7.2 Potential Benefits

Subjects may be cured of hepatitis C during the course of this study. Further, they may have decreased risk of HIV acquisition and may decrease or abstain from opioid misuse. They will contribute to the body of scientific research on treatment of hepatitis C and prevention of HIV in high-risk populations and therefore may confer long term benefits on other patients within their community. It is possible that subjects will receive no benefit from the study participation.

8 Stored Samples and Future Research

We will study the viral and host immunity to HCV and HIV in all patients. The results will be used to characterize each individual with regards to immune status and chronicity of disease. Studies on research samples may include the following:

A] HCV genome sequencing may be performed on plasma using the protocol as described and compared for variability and relatedness of sequences.

B] We will screen sera from all patients for differential expression of protein using multiplex cytokine arrays, which has the capability of detecting several different cytokines and other biologically relevant proteins.

C] We will perform detailed phenotypic and functional evaluation of immune cell types in the periphery. This will help us in determining the nature of antiviral immune responses in patients who are chronically infected, achieve SVR and acquire new HCV and HIV infections. Determination of specific immune defects in these individuals are important milestones in deciding future therapeutics and protective immunity to reinfection. Exhaustion and activation markers on T, B and NK cells will be quantified. Specific immune responses against pooled HCV peptides will be performed using an ELISPOT assay and/or flow cytometry.

Future use of the specimens will be based on the scientific merit of the investigation and would be decided by the Principal Investigator. They would be related to the study of HCV and/or HIV. Other investigators may wish to study these samples and/or data. In that case, IRB approval must be sought prior to any sharing of samples and/or data. Any clinical information shared about the sample would similarly require prior IRB approval. If approved, and once a Material Transfer Agreement (MTA) has been established, the study team may send de-identified samples to the collaborators. Investigators will use stored samples only for research.

8.1 Intended Use:

Some blood samples may be stored for future analysis in this research study. These samples will be stored by the IHV researchers and may be used in future research to learn more about HCV and HIV, the immune system and/or other related medical conditions. The blood will be used over time to gain a better understanding of the pathogenesis of HCV and HIV. Genetic testing will be performed. Different analytical and laboratory methods will be employed including but not limited to: PCR, ELISA, ELISPOT and immunohistochemistry; RNA/DNA, cytokine and antibody quantitation; viral particle detection and identification of genetic markers. The consent will include language for specimen storage.

8.2 Storage:

Samples will be kept in secure facilities with limited access. Samples and data will be stored using a unique identifier. Only investigators and study staff will have access to the samples and data.

GMA Data - Electronic data will be stored on secure password-protected computers.
UMB has an executed Collaboration Agreement dated 5/1/18 with the National Institute on Drug Abuse (NIDA), National Institutes of Health (NIH) and will share some data as specified in the agreement with our scientific research partners at NIH. There will be no particiant identifiers in the shared data.

8.3 Tracking:

Extra blood samples will be stored using a unique identifier that only the study team can trace back to the participants. These stored samples as well as a linkage file will be maintained in a database that will be managed by the Investigators and/or Study Coordinators and will be maintained on the IHV server. This database will also be stored on the password-protected computer of the Lead-Investigator/Study Coordinator in an encrypted and/or password-coded file.

8.4 Disposition at the Completion of the Protocol:

At the completion of the protocol (termination), samples and data will either be destroyed, or after IRB approval, transferred to another existing protocol. Final disposition of any samples cannot be done without written permission from the PI.

8.5 Reporting the Loss or Destruction of Samples/Specimens/Data to the IRB:

- Any loss or unanticipated destruction of samples or data resulting in a violation that compromises the scientific integrity of the data collected for the study will be reported to the IRB.
- Participants may request at any point not to have their samples stored. In this case, the Principal Investigator will destroy all known remaining samples and report what was done to

both the participant and to the IRB. This decision will not affect the subject's participation in any other protocols.

Generally, the results from the research stored samples will not be given to the participant's primary care provider or appear in the medical record. This is because the test results, unlike routine medical testing, may be experimental or preliminary. The relevance of these tests to direct patient care may be unknown. At the participant's request, the results of any research tests will be discussed with the primary care physician by the Investigators.

9 Assessment of Safety

As this is an observational study involving standard of card treatment, with interventions limited to non-standard fo care blooddraws and epidemiologic information collection, safety issues are not expected. Only those reportable Adverse Events (AEs) related to the research procedures will be reported. The PI will review the safety data and report any unexpected events to the IRB along with annual continuing review

9.1 Recording/Documentation

At each contact with the patient, information regarding adverse or unexpected events related to research procedures 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 and data collection tools. Source documents will be reviewed in a timely manner by the research team.

9.2 Definitions

Adverse Event: Any untoward medical occurrence in a human subject, including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

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

9.3 Reporting Protocol deviations, AEs and Deaths

Anticipated deviations in the conduct of the protocol will not be reported to the IRB unless they occur at a rate greater than anticipated by the study team. Expected adverse events will not be reported to the IRB unless they occur at a rate greater than that known to occur in those having phlebotomy procedures normally. If the rate of these events exceeds the rate expected by the study team, the events will be classified and reported. Deaths related to the natural history of hepatitis will be reported at the time of continuing review (see annual reporting to the IRB).

9.3.1 Expedited Reporting to the IRB

Any reportable new information (RNI) will be reported to the IRB within 5 business days. This includes:

1) Information that indicates a new or increased risk, or a safety issue.
2) Any harm experienced by a subject or other individual, which in the opinion of the investigator are unexpected and probably related to the research procedures.
3) Non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance.
4) Failure to follow the procedure due to the action or inaction of the investigator or research staff.
5) Breach of confidentiality.
6) Change to the protocol taken without prior IRB review to eliminate an apparently immediate hazard to a subject.
7) Incarceration of a subject in a study not approved by the IRB to involve prisoners.
8) Complaint of a subject that cannot be resolved by the research team.
9) Premature suspension or termination of the research by the sponsor or the investigator.
10) Audit, inspection, or inquiry by a federal agency.
11) Written reports of study monitors.

9.3.2 Waiver of Reporting Anticipated Protocol Deviations, Expected non-UP AEs and Deaths

Deviations in the protocol that do not rise to the level of serious or continuing non-compliance, and unanticipated or adverse events that are NOT serious, unexpected AND related to research protocols need not be reported in an expedited manner to the IRB. Rather, such RNI should be reported as a group at the time of annual renewal (see below).

9.4 Annual Reporting to the IRB

The following items will be reported to the University of Maryland IRB in summary at the time of Continuing Review:

- Serious adverse events or deaths that are not related to the research
- All adverse events associated with research including expected AEs Protocol deviations. This includes AEs related to phlebotomy within 48 hours of procedure.
- Serious, continuing, and minor non-compliance
- Any trends or events which in the opinion of the investigator should be reported
- Any study particpants incarcerated while on active HCV treatment that were provided their remaining HCV medications in the jail/prison

9.4.1 Type and Duration of the Follow-up of Subject after Adverse Events

All SAEs and non-serious AEs identified in this study will be followed until resolution or until the PI judges the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that the follow-up may be required for some events after the participant discontinues participation from the study. These events will be reported to the IRB annually.

10 Withdrawal of a Subject

A participant may withdraw from the study at any time. As part of their duties to ensure that research participants are protected, the IRB, IHV, or other government agencies may discontinue the study at any time. Voluntary withdrawal from the protocol may occur at any time at the request of either the participant or the PI. If a request is made to withdraw from the protocol, all further planned study procedures will be immediately cancelled and further follow-up will be terminated. Samples and data collected already collected may be used.

If a patient becomes pregnant during the course of the study, the patient will be discontinued from the study.

10.1 Return of Withdrawn/Removed Subjects

A participant who has withdrawn may not return to the study.

11 Remuneration Plan for Subjects

Participants will not be renumerated for receiving HCV treatment.

Participants will not be renumerated for standard of care PrEP or buprenorphine.

Participants will receive $25 remuneration as gift cards at those visits where HIV risk assessment and stored sample blood draws are completed. Those 7 visits are Screening, Week 4, Week 12, Week 24, Week 48, Week 72 and Week 96 only. For adherence visits for PrEP which DO NOT coincide with HIV risk assessment or stored sample visits, participants will receive $25 reumeration as gift cards for those visits. This would be a maximum of 6 additional visits at $25/visit. We will encourage combined visits.

Participants who choose to enroll in the GMA will be renumerated as follows:

Compensation for GMA data collection	A) Weeks 1-24 Participants can receive a total of $480 between weeks 1-24 for answering random daily prompts based on how many prompts they answer in each week: Answering 1-7 prompts/week = $5 Answering 8-14 prompts/week = $10 Answering 15-21 prompts/week = $15 Answering 22-28 prompts/week = $20 B) Weeks 25-48	Up to $920.00

	Participants can receive a total of $240 between weeks 25-48 for answering random daily prompts based on how many prompts they answer each week: Answering 1-3 prompts/week = $5 Answering 4-7 prompts/week = $10 C) End of Study Week 48 Participants can receive up to $200 for returning the smartphone in working condition at Week 48, to be pro-rated by week for those participants who do not complete 48 weeks of the study,	

12 Monitoring

As this is an observational study with intervention limited to blood and epidemiologic data collection, safety issues are not expected. PI and the study team will conduct regular monitoring of safety on a weekly basis and report to the IRB as specified in section 9.

13 Statistical Considerations

13.1 Description of the Analyses

The primary outcome is achievement of SVR12 in phase 1 (first 100 enrolled participants). The primary analysis of efficacy for phase 1 is intention-to-treat for the proportion of patients who achieve SVR along with exact two-sided 95% confidence intervals, overall and by sub-categories. All patients who receive at least one dose of direct acting antiviral are included in the intention-to-treat analysis and patients without follow-up data are considered to have treatment failure. Chi-squared or Fisher's exact text will be used to assess the association of SVR12 with baseline characteritics such as HIV-status, as well as on treatment factors such as medication adherence and OST status. Percentage and standard error will be calculated for each of the secondary outcome of PrEP and buprenorphine including uptake, adherence, and retention. In phase 2, participants without recent IDU (opioid misuse within 1 year but not within 3 months) will be compared to patients with recent IDU, and the impact of collocated OST vs non-collocated OST will be assessed.

13.2 Sample Size Justification

Based on the available DAA drugs, we expect to be able to treat up to 200 patients for HCV, with primary efficacy analysis after the first 100 enrolled participants (phase 1). The SVR of the general US population for HCV-infected and non-injection drug users is estimated at >90%. We target in our population of injection-drug users no greater than a ± 10% SVR difference from the standard 90% SVR. For the primary objective, we will have 85% power to reject the null hypothesis if the actual proportion of patients with SVR is 80% or higher at a 2-sided, α=0.05 significance level.

14 Ethics/Protection of Human Subjects

14.1 Informed Consent Process

Informed consent is a process where information is presented to enable persons to voluntarily decide whether or not to participate as a research subject. It is an on-going conversation between the human research subject and the researchers, which begins before consent is given and continues until the end of the subject's involvement in the research. Discussions about the research will provide essential information about the study and include: purpose, duration, procedures, alternatives, risks and benefits. Subjects will be given the opportunity to ask questions and have them answered.

The subjects will personally sign and date the informed consent document prior to undergoing any research procedures. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. Consenting process will be documented in the record. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.2 Illiteracy and Consenting

As the majority of the patient populations from which the study participants are drawn are literate, written consent will be obtained. Per UMB IRB policy, for participants unable to read, the written informed consent and any other written information will be read and explained to the participant by the person obtaining consent. An impartial third party will be present for the entire consent process. Once the subject has orally consented, the participant and witness will sign the consent form.

14.3 Subject Confidentiality

All records will be kept confidential to the extent provided by federal, state and local law. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records. Records will be kept locked and all computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, FDA, the Joint Commission or the HHRP.

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APPENDIX B: Study Schedule

					M1	M2	M3	M6	M9	M12	M18	M24
HCV Treatment	**Screening**	**Day 0**	**Week 2**	**Week 3**	**Week 4**	**Week 8**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**Week 72**	**Week 96**
MD Visit	X	X*			X*	X*	X*	X*				
HCV SOC Labwork	X				X		X	X				
HCV RNA	X				X		X	X		X	X	X
HCV Adherence			X		X	X	X					
Stored Samples	X				X		X	X		X		X
Fibroscan	X							X		X		X
PrEP Retrospective Questionnaire										X	X	X
PrEP**		**Day P0**			**Week P4**		**Week P12**	**Week P24**	**Week P36**	**Week P48**		
MD Visit		X			X		X	X	X	X		
Adherence					X		X	X	X	X		
Labwork		X			X		X	X	X	X		
Buprenorphine***		**Day B0**	**Week B2**		**Week B4**	**Week B8**	**Week B12**	**Week B24**	**Week B36**	**Week B48**		
MD Visit		X	X		X	X	X	X	X	X		
Urine Buprenorphine			X		X	X	X	X	X	X		
Assess Retention			X		X	X	X	X	X	X		
Risk Monitoring	**Screening**	**Day 0**	**Week 2**	**Week 3**	**Week 4**	**Week 8**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**Week 72**	**Week 96**
Epidemiologic Survey	X											
HCV PRO	**X**						X	X				
HIV Risk/SEP Assessment		X			X		X	X		X	X	X

Urine Drug Screen	X				X		X	X		X	X	X
HIV 4th gen	X				X		X	X		X	X	X
AUDIT-C	X							X		X		X
ACE								X				
GMA Assessment**												
GMA Training and Cell Distribution		X										
Adheence Packet -4		X										
Adherence Packet-2					X		X	X		X		
Return Cell Phone										X		

*Study participants will be offered PrEP and buprenorphine at every MD visit if have not currently uptaking
**PrEP uptake is optional. Day P0 can be on any day from Day 0 to Week 24 of HCV treatment.
***Buprenorphine uptake is optional. Day B0 can be on any day from Day 0 to Week 24 of HCV treatment.
****GMA participation is optional.

Appendix C: Epidemiologial Suvrey (IDU in last 3 months)

Appendix D: HIV Risk Assessment

Appendix E: AUDIT-C

Appendix F: HCV Patient Reported Outcomes Survey

Appendix G: Geographic Momentary Assessment (GMA) Daily Phone Surveys

Appendix H: Adverse Childhood Experiences (ACE) Questionairre

Appendix I: GMA Adherence Packet 5

Appendix J: Epidemiology Survey (Non-IDU with last 3 months)

Appendix K: PrEP Retrospective Questionnaire