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FULL TITLE: Rapid HCV Test and Treat to increase HCV treatment uptake among people who use drugs (RAPID-HCV)

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1 SYNOPSIS

TITLE: Rapid HCV Test and Treat to increase HCV treatment among people who use drugs (RAPID-HCV)

DESIGN: Open label multicenter, phase IV randomized trial of a test and treat strategy with peer enhancement for HCV treatment at drug treatment programs versus standard of care referral for HCV treatment.

DURATION: Participants will be on study for up to a total of 12 months after HCV treatment initiation (treatment and observation period).

SAMPLE SIZE: 124 HCV infected participants will be enrolled in the study from five drug treatment programs in four cities (Baltimore Maryland, Birmingham Alabama, San Francisco California and Toronto Canada). Up to 15 peers and 45 drug treatment program staff members (for in-depth interviews only) will be enrolled across all sites. Total enrollment up to 184 participants.

POPULATION: People who use drugs enrolled in drug treatment programs with confirmed ongoing HCV infection.

All participants ≥ 18 years of age enrolled at study drug treatment sites who have ongoing HCV infection (as determined through study testing procedures).

STUDY DRUG AND DURATION OF TREATMENT: Subjects will receive GLE/PIB fixed-dose combination (300 mg/120 mg) QD for 8 weeks.

2 INTRODUCTION

2.1 Background and Rationale

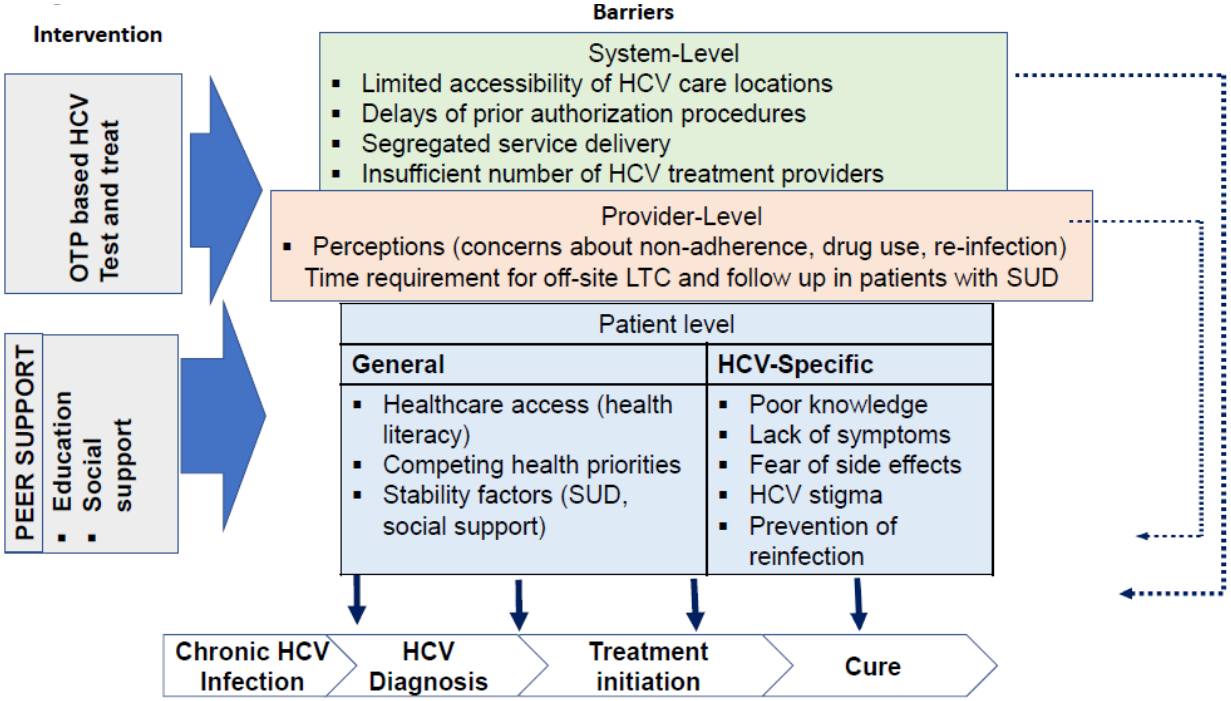
Why Is This Study Being Conducted?

Hepatitis C virus (HCV) infection is a major public health challenge and is associated with significant morbidity and mortality.[1] The World Health Organization (WHO) has called for elimination of HCV as a public health challenge by the year 2030. The WHO elimination goals include a 90% reduction in HCV incidence and a 65% reduction in HCV related mortality by 2030 relative to 2015 rates.[2] However, the United States is experiencing increases in HCV incidence directly attributable to injection drug use with the steepest increase in incidence since 2011.[3,4] Although people who use drugs (PWUD) have disproportionately high rates of HCV infection, rates of HCV treatment remain low among PWUD.[5,6] Once initiated on HCV therapies, PWUD have been demonstrated to achieve high rates of HCV cure.[7]

HCV treatment uptake among PWUD, the core of the HCV epidemic, remains low due to multiple interrelated barriers at the level of the patient, the provider, and the system.[8-10] Patient-level barriers include poor knowledge related to HCV and its treatment and absence of symptoms. These issues are compounded by general barriers to health care access (e.g., not having insurance or a primary care provider), competing comorbidities, which may require more immediate attention, and factors that impede stability, such as ongoing Substance Use Disorder (SUD), unemployment, and lack of transportation.[11-13] In many parts of the world, the major structural barrier of medication cost has been reduced through insurance coverage for HCV treatment by payers and removal of insurance coverage restrictions related to drug use or liver disease stage. Beyond cost, additional structural barriers include insufficient HCV treatment locations. HCV care has historically been delivered in specialist settings thus segregating HCV treatment from other services that PWUD utilize including those received at opioid treatment programs (OTPs).

Drug treatment programs such as OTPs routinely provide services for PWUD, with many patients accessing care at these settings multiple times a week. The structure of care provision at OTPs including observed dosing of opioid agonist therapies, offers a unique infrastructure upon which to layer HCV treatment. In addition, simplification of HCV treatment protocols endorsed by the major guidelines including the AASLD/IDSA[14] provide an opportunity to implement HCV treatment in non-traditional settings. We propose to evaluate effectiveness of an HCV test and treat strategy at OTPs, a venue with a captive audience of patients with untreated HCV infection. To support the effectiveness of this strategy, we will use a validated protocol to identify and train peers at OTP sites to support HCV treatment engagement and reinfection prevention of PWUD recruited at these sites. The interventions we propose to test will target barriers at different levels and thus impact multiple steps in the HCV care continuum from linkage to care to cure (Figure 1).

Figure 1: HCV Treatment Barriers



2.2 Clinical Hypothesis

An HCV test and treat strategy, defined as immediate offer of and access to HCV treatment after testing HCV positive enhanced by peer support, will be associated with higher rates of HCV treatment initiation and cure compared to standard of care (SOC) referral to off-site HCV treatment.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The study aims to assess the effectiveness of an HCV test and treat strategy with peer enhancement compared to standard of care referral.

3.2 Primary Endpoint

The primary effectiveness endpoint is:

Treatment initiation: Proportion of participants who start HCV treatment (in initial test and treat arm versus standard of care referral arm) within 12 weeks of randomization.

3.3 Secondary Endpoints

1) HCV treatment completion: Proportion of those initiating treatment who complete HCV treatment defined as taking more than 90% of prescribed treatment course by expected end of treatment date.

2) SVR 12: Proportion of participants with HCV RNA <15 IU/ml between 10 and 36 weeks after end of treatment in each randomization arm.

3) Time to HCV treatment initiation after randomization.

3.4 Exploratory Endpoints

1) Impact of test and treat versus standard of care referral on proportion of participants with change in substance use assessed by self-reported drug use in the preceding 30 days and urine toxicology at recruitment screening, end of HCV treatment, and post-treatment weeks 12, 24, and 36. Participants who do not start HCV treatment will be assessed at weeks 12, 24, and 36 post-randomization.

2) Impact of test and treat versus standard of care referral on subsequent substance use disorder treatment engagement-Proportion of expected weekly OTP visits actually attended, based on participant's OTP treatment plan.

3) Proportion of patients in the standard of care arm who are not offered treatment within 6 months (24 weeks) of randomization.

4) Proportion of patients in the standard of care arm who do not initiate treatment within 6 months (24 weeks) of randomization and subsequently initiate HCV treatment after study cross over to intervention arm.

5) Patient reported outcomes, quality of life measures, and patient satisfaction with test and treat model versus standard of care referral will also be assessed.

6) Proportion of participants with grade 3 or greater adverse events (AEs) in test and treat model versus standard of care referral.

4 INVESTIGATIONAL PLAN

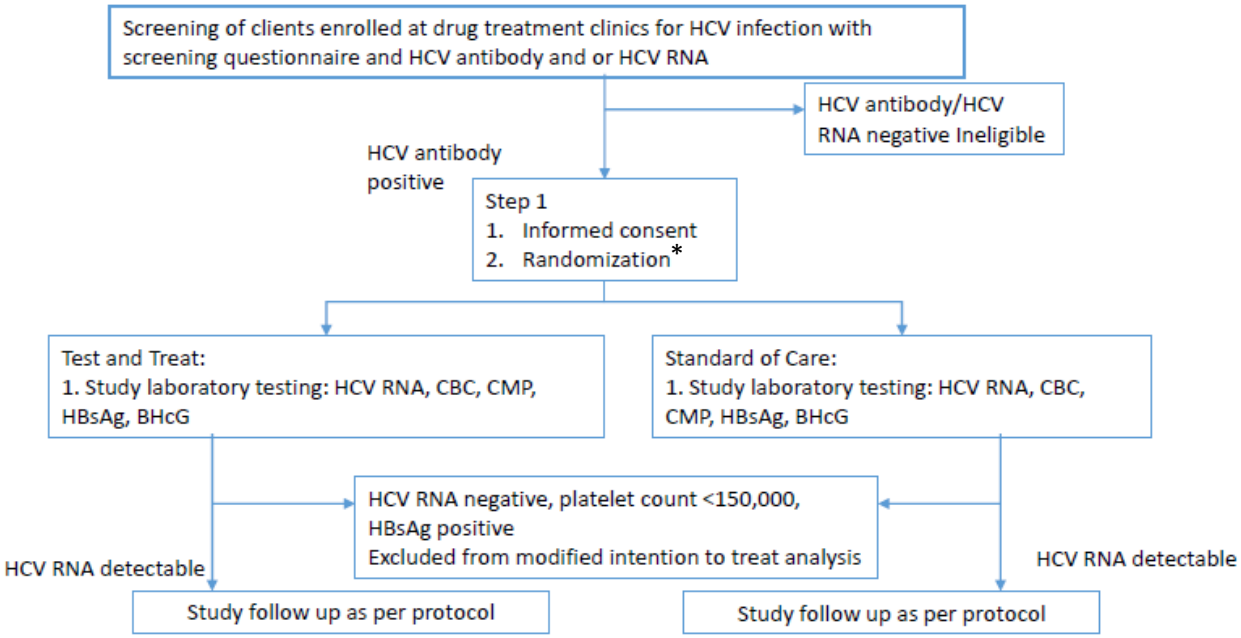
4.1 Overall Study Design and Plan

This is an open label, multicenter, phase IV randomized trial to assess the effectiveness of an HCV test and treat strategy with peer enhancement compared to standard of care referral.

The study is designed to enroll approximately 124 HCV infected subjects at 4 drug treatment program sites in the US and 1 drug treatment program site in Canada.

We will also characterize the processes of implementation of peer supported on site HCV treatment at the drug treatment clinics including adoption, fidelity, drug treatment clinic staff acceptability, and drug treatment clinic workflow integration and congruence.

Figure 2: Study Schema



* Study laboratory testing (HCV RNA, CBC, CMP, HBsAg, BHcG) may be collected prior to randomization.

Test and treat strategy with peer support: Consistent with the approach in substance use self-help groups such as narcotics anonymous, the intervention will include support for HCV treatment initiation and completion from true peers (PWUD who have previously engaged in HCV treatment).

Peer Mentor selection and training: Many OTPs utilize peers as an element of substance use recovery. Each site will identify individuals with a history of drug use who have been treated for HCV and demonstrate good communication and interpersonal skills to serve as peers. These individuals may be referred to study staff by OTP staff. They will then be offered participation in the study and be consented to participate in the study as peers, and will undergo a tailored validated training (up to 5 hours) developed and successfully utilized in the CHAMPS trial[15]. Trainings will include in-depth discussions of HCV, HCV treatment and prevention of reinfection and skill development such as effective mentoring, active listening skills, facilitation, the importance of confidentially, and harm reduction including overdose prevention. These trainings are divided into 5 modules which can be watched independently by peers. Modules are designed to be engaging with activities which the peer will complete during the module and then discuss with site research assistants during check-in sessions. Peers will be assessed to ensure they have mastered required competencies to function effectively as a peer prior to being permitted to serve in this role.

In the event a peer drops out, sites will be asked to identify other peers who have successfully completed HCV treatment who are interested in participating in the study as a peer. They will then go through the training process and undergo evaluation to ensure that they have mastered the required

competencies prior to being permitted to serve as peer.

The peers will meet and engage with participants in the test and treat strategy at the time of randomization, throughout treatment, and up to assessment of SVR 12. The key role of the peers will be to provide information, enhance motivation, and role model behavioral skills required for HCV treatment initiation, completion, and reinfection prevention.

Standard of care referral: Referral to off-site partner site with provision of clinic information for scheduling.

4.2 Study Procedures

4.2.1 Hepatitis C Diagnosis and Recruitment Screen

Prior to study roll out, site investigators will meet with drug treatment center leadership to outline procedures for offering study participation to drug center clients. The OTP will facilitate HCV antibody testing and/or HCV RNA testing through rapid testing or phlebotomy. Prior to study enrollment, participants will complete an initial screening questionnaire, which will explore if the participant has previously been diagnosed with HCV, and if previously diagnosed, previously treated for HCV with oral direct-acting antiviral (DAA) therapy. Individuals who report previous HCV treatment with oral DAA therapy will not be eligible for study enrollment. Potential participants will also be asked about their current medications to ensure they are not currently taking any medication prohibited by the study (see Sections 5.1 and 5.3). Individuals who report taking a study-prohibited medication will not be eligible for study enrollment. These screening questions will be mixed with other questions to ensure that participants remain unaware of study eligibility criteria. Individuals who are HCV antibody or HCV RNA positive on testing and remain study eligible after completing the screening questionnaire will be offered enrollment into the study and if willing, go through the process of informed consent.

4.2.2 Informed Consent

Each participant must give consent according to local requirements after the nature of the study has been fully explained. The informed consent form (ICF) that is used must be approved by the Institutional Review Board (IRB) and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current International Conference for Harmonization (ICH) and Good Clinical Practice (GCP) guidelines and applicable regulatory including IRB policy and requirements.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded. After having obtained the consent, a copy of the ICF must be given to the participant.

4.2.3 Demographic and Medical History

After signing consent, participant's name, date of birth, age (calculated), sex, primary and secondary forms of contact, address, race, and ethnicity will be collected. Medical history will be collected by participant interview. Participants will be asked to provide all medical history to the best of their recollection, and then will be asked specifically about the following medical history items that impact

eligibility: Presence of liver cirrhosis or history of decompensated liver disease or liver cancer, pregnancy, previous HCV treatment with oral DAAs, history of hepatitis B infection.

4.2.4 Concomitant Medication Documentation

All concomitant medications and supplements as of Day 0 will be recorded.

4.2.5 Pregnancy Test

All participants will be asked to provide information determining childbearing status. Females who are post-menopausal (absence of menses for 12 months or greater) or who have had a hysterectomy are considered not to be of childbearing potential. Any females not meeting these criteria are considered to be of childbearing potential and will have a point of care dipstick urine or serum beta human chorionic gonadotropin (HCG) test performed. Pregnant women will not be enrolled in this study.

Females of childbearing potential will be cautioned against getting pregnant or attempting to get pregnant during this study. Requirements for ongoing contraception are noted in protocol section 5.2.

4.2.6 Vital Signs

Height, weight, temperature, pulse, respiratory rate and blood pressure will be collected at the study site.

4.2.7 Patient Reported Outcomes (PRO) and Quality of Life (QOL) Measures

We will utilize validated measures to assess patient reported outcomes and will also qualitatively assess satisfaction with HCV care received in both intervention and SOC arms. We will utilize the validated Eq 5d-5l[16], validated PHQ-8[17], GAD-7[18], AUDIT C[19], modified addiction severity index, MOS social support scale, Health efficacy and HCV stigma scales. We will also qualitatively assess participant perception of their HCV care among a purposively sampled group of patients who did and did not initiate HCV treatment in intervention (n=20) and standard of care (n=20) across the five OTPs. Participants will be offered interviews starting approximately 6 months post-randomization. In-depth interview guides will be designed to focus on experiences with HCV treatment, barriers and facilitators of HCV treatment initiation and completion.

4.2.8 Randomization

Randomization will occur separately at each OTP. Randomization will take place on day 0 after recruitment screening activities have been performed and the Investigator or designee has determined that the participant is eligible based on information that is available. Day 0 laboratory tests including blood HCV RNA, complete blood count (CBC), comprehensive metabolic panel (CMP), hepatitis B surface antigen (HBsAg), and urine/serum beta HCG, may not be available at the time of randomization and participants may be randomized without this information. Randomization will be built into the study REDCap database. It may not be known at screening whether participants have detectable HCV RNA or not. All participants will be randomized in a 1:1 ratio to test and treat strategy or standard of care referral. Participants who are found to have an HCV RNA that is not detectable, HbsAg positive or a platelet count that is <150,000 will not continue in the study, and will be referred to an offsite location for care.

4.2.9 Study Arms

Intervention – Test and Treat strategy: This will consist of a meeting (in person, by phone or over video) with a trained peer mentor who will meet with the study participant after randomization to communicate information about HCV in a manner that takes into account an understanding of experiences with HCV and care access faced by people who use drugs, the potential harms of untreated HCV and the benefits of HCV treatment.

Peer Training, Monitoring, and Quality Assurance. Peers will receive training modelled on our previous experience training peers for HCV treatment support. The training will be provided as modules. Topics to be addressed in the modules are: 1) Power of peer mentoring and key values including confidentiality and respect for all persons; 2) Tools for effective communication; 3) HCV disease and substance use disorder including importance of adherence to medications/visits; 4) Self-care in the peer-mentor role; 5) review of patient tracking tools. Peers will also have an individual training session. Individual sessions will prepare the peer for their peer support role including building communication skills to enhance conversations to support HCV care engagement. Peers will be trained to improve their communication skills with a focus on: 1) providing accurate information; 2) working with patients on goal setting for HCV treatment adherence; and 3) identifying barriers to retention in care. We will ensure peers have demonstrated competency in all of their tasks through knowledge and performance assessments as judged through role-plays.

Peer support and care coordination tasks. Peers will be responsible for maintaining contact with patients in the test and treat arm. They will also complete adherence and food use with medication surveys at weekly contacts. He or she will also communicate the need to return for results of follow up testing and follow through with recommended treatment. The Peer will also communicate to the patient the expected timing of follow up appointments at the drug treatment center and will offer support for the duration of HCV treatment. Up to 15 peers will be enrolled in this study.

The treatment initiation visit at the drug treatment center will depend on the standard amount of time it takes to get results of laboratory testing back to the drug treatment center site. We expect this to be 3-5 days.

The peer will contact the patient 2 days before and the day before the scheduled appointment to remind that participant about the appointment.

Peers will have a standard protocol for at least weekly phone contact with participants through post-treatment week 12, and will be available to answer participant questions as needed. Peers will maintain a log of peer contact, which will be submitted to research program staff weekly.

Peers will have access to drug treatment clinic staff for support with trouble shooting any arising matters.

Peers will submit weekly logs of participant contact to the research program coordinator and meet as a group (both peers and research program coordinator at each site, either virtually or in person) to review best practices and address any issues or questions related to effective performance as a peer.

If the participant does not want to work with the assigned peer, they can choose not to receive peer services.

HCV treatment initiation. At the treatment initiation visit, if still eligible for the study after all Day 0 results are available (detectable HCV RNA, platelet count >150,000, not pregnant) the patient will be offered immediate initiation of HCV treatment.

HCV treatment will be initiated at the drug treatment center. Participants will be provided a 4-week supply of glecaprevir/pibrentasvir (GLE/PIB) combination. For patients who report living and other situations that pose barriers to safe storage of a 4-week supply of medications, individual drug treatment centers will develop processes for providing GLE/PIB in quantities that can be safely stored by the participant.

At the treatment initiation visit, participants will be given a follow up appointment for 8 weeks after treatment initiation (expected end of treatment) with designated drug treatment center staff.

Standard of Care Referral to Offsite Location: Participants randomized to standard of care arm will be referred to an offsite HCV treatment site.

Using a signed release of medical information form, research staff will follow up with the referral site to see if the patient scheduled and subsequently attended an appointment and collect information on subsequent progress along the HCV care continuum.

If the patient is confirmed to have scheduled the appointment, study staff will contact the evaluating physician to make them aware that the study may provide GLE/PIB for HCV treatment.

Participants in the standard of care arm who do not initiate HCV treatment within 6 months (24 weeks) after randomization and still meet study eligibility criteria upon rescreen will be offered HCV treatment at the OTP site via rollover to the Intervention Arm.

Any participant that does not clear HCV infection will be linked to repeat HCV treatment and care at an offsite HCV treatment location through standard of care. There are approved regimens available to treat patients who do not achieve cure with first line treatment.

4.2.10 Intervention Fidelity Assessment

Peers will maintain logs of contact with participants randomized to the intervention arm. Peers will submit weekly logs of participant contact to site study research program coordinators.

4.2.11 Assessment of implementation outcomes

The well validated Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework[20] will be used to guide evaluation of implementation outcomes of peer enhanced HCV treatment at OTP sites using its dimensions; reach and effectiveness, which operate at the individual level of those intended to benefit; and adoption and implementation which focus on staff and setting levels. We will focus on acceptability of the peer enhanced drug treatment center based HCV test and treat strategy, barriers and facilitators of implementation success and congruence with drug treatment

clinic workflow. In-depth interviews will focus on exploring how peer supported drug treatment clinic based HCV treatment may become embedded in routine clinical practice in drug treatment settings. We will utilize a mixed methods assessment including quantitative survey data from patients (collected through clinical trial), and qualitative in-depth interviews (IDI) with drug treatment clinic leadership and staff (n=45) and program peers (n=15) across five sites.

Setting and population: The focus of this assessment is individuals implementing and being affected by implementation of peer-supported drug treatment clinic based HCV treatment. We will utilize the RE-AIM framework for this assessment.

Table 1: Summary of Implementation Outcomes Using the RE-AIM Framework

Component	Research Question	Assessment Method(s)	Outcome(s) of Interest	Sampling of qualitative interview content
Reach	Who received the peer enhanced drug treatment center based HCV test and treat intervention?	Study data Patient in depth interviews (IDI)	• Proportion of study participants who initiated HCV treatment. • Characteristics of those who initiated vs. those who did not initiate HCV treatment	Barriers and facilitators to HCV treatment initiation What components of the intervention were most effective (patients)
Effectiveness	What impact did the intervention have on outcomes?	HCV treatment initiation (Study data)	• Proportion of study participants who initiated HCV treatment in intervention compared to SOC arm.	--
Adoption	Did the patients, peers and drug treatment center adopt the intervention?	Study data, peer contact logs, OTP staff and peer surveys, IDI with providers, staff, peers	• Frequency of contacts between peers and patients. • Proportion of patients who previously failed to and subsequently cross over and initiate HCV treatment	Barriers and facilitators to adoption (intervention uptake), steps to enhance uptake; perceived need for intervention, perceived fit in current care structure (peers, drug treatment clinic staff, clinic leadership)
Implementation	Was the intervention	Standardized fidelity	• Adherence to intervention protocols (Fidelity)	Perceptions of the most effective components of the

	delivered as intended?	assessment form, IDI	• Dose frequency of peer contact with patient. • Frequency of HCV medication pick-up at OTP	intervention (peers, providers, clinic staff, leaders),

4.2.12 Adjustments for COVID related restrictions

Study specific activities including screening, consenting, survey administration will have the option of being performed remotely by phone or video visits with research staff. All study activities that must be done in-person (sample collection, study medication dispensation) for participants in both arms may occur during the participant's regularly scheduled OTP visits. No additional research-only visits to OTP will be needed.

5 STUDY ACTIVITIES

5.1 Inclusion and exclusion Criteria

Inclusion criteria: Participants must meet all of the following inclusion criteria to be eligible for participation

- Ability and willingness of participant to provide written informed consent
- Men and women age ≥18 to ≤70 years at study entry
- HCV antibody positive/Detectable HCV RNA
- HCV treatment naïve (no prior treatment with an approved or investigational oral DAA therapy)
- Negative pregnancy test at screening or at the day of treatment initiation (females of childbearing potential only)
- If co-infection with Human Immunodeficiency Virus (HIV) is documented, the subject must be anti-retroviral treatment (ART) naïve with CD4 T cell count >500 cells/mm3 OR on a stable ART regimen (containing only permissible ART – Raltegravir; dolutegravir; Rilpivirine; Elvitegravir/cobicistat; Tenofovir disoproxil fumarate; Tenofovir alafenamide; Emtricitabine; Lamivudine and/or Abacavir, bictegravir)

Exclusion criteria: Subjects who meet any of the following exclusion criteria are not to be enrolled in this study

- Women who are pregnant or breastfeeding, or considering becoming pregnant during the study and for 30 days after the last dose of study drug
- Known allergy/sensitivity or any hypersensitivity to components of study drugs or their formulation
- Current or history of decompensated liver disease (including but not limited to encephalopathy, variceal bleeding, or ascites) prior to study entry

- History of hepatocellular carcinoma (HCC)
- Any history of active Hepatitis B or positive HBsAg test
- Platelet count < 150,000/mm^3
- HCV RNA undetectable
- History of clinically significant abnormalities or co-morbidities that make the subject an unsuitable candidate for this study, in the opinion of the investigator.
- Women of childbearing potential that are not practicing at least one specified method of birth control (refer to Section 5.2) that is effective from Study Day 1 through at least 30 days after the last dose of study drug.
- Subject is currently taking any of the following prohibited medications:
    - Red yeast rice (monacolin K), St. John's Wort
    - Carbamazepine, Dabigatran, efavirenz, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin
- Subject is not able or willing to safely discontinue the prohibited medications or supplements listed below at least 14 days prior to the first dose of GLE/PIB:
    - Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with the study drug. Subjects receiving these statins should either (a) switch to pravastatin or rosuvastatin at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of study drug or (b) may interrupt statin therapy throughout the treatment period beginning at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of study drug and until 14 days after the last dose of study drug, based on investigator's judgment. If switching to or continuing pravastatin or rosuvastatin, it is recommended to reduce the pravastatin dose by 50% or limit the rosuvastatin dose to 5 mg QD when taking with the study drug.
    - Astemizole, cisapride, terfenadine
    - Ethinyl estradiol

5.2 Contraception Recommendations

Contraception Requirements for Females:

Postmenopausal is defined as:

- Age > 55 years with no menses for 12 or more months without an alternative medical cause.

If female, subject must be either post-menopausal, permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy) or a woman of childbearing potential (WOCBP) and must practice at least one of the following methods of birth control, throughout the study including 30 days after the last study drug dose is given.

- Contraceptives and/or hormonal replacement therapies containing only progestins (such as those containing norethindrone, desogestrel, or levonorgestrel) or those containing progestins

with non-ethinyl estradiol estrogens (e.g., esterified or conjugated) associated with inhibition of ovulation initiated at least 1 month prior to study Baseline Day 1.

- Bilateral tubal occlusion/ligation.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Vasectomized sexual partner(s) (the vasectomized partner(s) provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the trial participant).
- Male or female condom with or without spermicide.
- Cap, diaphragm or sponge with spermicide.
- A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier method).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject, (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

For male study subjects no contraception is required.

5.3 Prohibited Medications and Therapy

Subjects must not be taking any prohibited medications or supplements listed in Section 5.1 for at least 14 days prior to the first dose of any study drug and not use these during the entire treatment period and for 14 days following discontinuation of study drug.

Contraceptives and/or hormonal replacement therapies containing only progestins (such as those containing norethindrone, desogestrel, or levonorgestrel) or those containing progestin with non-ethinyl estradiol estrogens (e.g., esterified or conjugated) may be used with GLE/PIB at the discretion of the Investigator.

5.4 Prior and Concomitant Therapy

The investigator should confirm that a concomitant medication/supplement can be safely administered with study drug. Some medications may require dose adjustments due to the potential for drug-drug interactions (DDIs).

Any medication/supplement or vaccine (including over-the-counter or prescription medicines, vitamins and/or supplements) that the subject is receiving from the time of signing the consent through the Treatment Period must be recorded in the electronic case report form (eCRF) along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency. The investigator should review all concomitant medications for any potential DDIs.

Any questions regarding concomitant or prior therapy should be raised to the Sponsor Medical Contact.

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the Investigator or the Sponsor Medical Director.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Eligibility criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk.
- The subject becomes pregnant while on study drug and the investigator, after discussion with the subject, concludes that the benefit of continuing therapy does NOT outweigh the risk.
- Subject is significantly non-compliant with study procedures, which would put the subject at risk for continued participation in the trial.
- For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject. At a minimum (unless otherwise required by local regulations), 2 phone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation. If a patient is not reachable by phone a letter will be sent or visit conducted to the address on file to reestablish contact with the patient. The letter/visit will alert the patient of study team efforts to reach them as well as provide the viable contact methods the patient may use to contact the study team.

Sponsor may terminate this study prematurely, either in its entirety or at any site. The Investigator may also stop the study at his/her site if he/she has safety concerns. If the study terminates for safety reasons, the sponsor will promptly notify the Investigator.

Refer to Section 6.3 for additional discontinuation criteria relating to Toxicity Management.

5.6 Follow-Up for Subject Withdrawal from Study

In order to minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless they have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued clinical importance of their data even if they discontinue treatment with study drug early.

If, during the course of study drug administration, the subject prematurely discontinues (D/C) study participation, the procedures outlined for the applicable Premature D/C Visit in the Schedule of Events

(Appendix A) should be completed. Ideally, this should occur on the day of study drug discontinuation, but no later than 2 days after their final dose of study drug and prior to the initiation of any other anti-HCV therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment. All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The last dose of any study drug and reason for discontinuation will be recorded in the eCRF.

If a subject is discontinued with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

5.7 Study Drug

5.7.1 Identity of Study Drug

Information about the study drug to be used in this study is presented in Table 2.

Table 2: Identity of Study Drug

Study Drug	Manufacturer	Mode of Administration	Dosage Form	Strength
Glecaprevir/pibrentasvir	AbbVie	Oral	Film-coated tablet	100 mg/40 mg

Three tablets of GLE/PIB combination will be taken daily and should be taken at the same time each day. The study drug must be taken with food.

Glecaprevir/pibrentasvir combination tablets will be provided.

5.7.2 Packaging, labelling, storage and accountability of clinical trial supplies

Glecaprevir/pibrentasvir will be provided by AbbVie and should be dispensed under the supervision of the investigator or a qualified member of the study team including drug treatment center staff, or by a hospital/clinic pharmacist.

Participants will not be required to return any unused study drug. Study drug may not be relabeled or reassigned for use by other participants.

A designated person at the study site must receive the study drug shipment. That person must check that the supplies are in good condition and are complete as per the shipping records. Study drugs must be stored in a secure location with limited access. The study drug must only be dispensed according to the protocol and records must be kept detailing supplies received, dispensed to the participant, returned from the participant and returned to the sponsor or destroyed at site, as applicable.
Study staff must not open or count clinical trial supplies prior to dispensing.

Study drug should 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.

Glecaprevir/pibrentasvir should be stored according to the product label.

Participants should ensure that the study drug is stored securely away from children and in dry conditions. The study drug should be kept in the original packaging.

5.8 Protocol Deviations

The Investigator is responsible for complying with all protocol requirements, written instructions and applicable laws regarding protocol deviations. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified), the Investigator is responsible for notifying IRB, regulatory authorities (as applicable) and the Sponsor.

5.9 Study Labs

The study-specific laboratory tests being conducted are HCV RNA, complete blood count (CBC), comprehensive metabolic panel (CMP), hepatitis B surface antigen (HBsAg), urine drug testing, and urine/serum beta HCG. These tests are able to be submitted to the study site's local laboratory of choice.

The chemistry tests required in the CMP are alanine aminotransferase (ALT/SGPT); albumin:globulin (A:G) ratio; albumin, serum; alkaline phosphatase, serum; aspartate aminotransferase (AST/SGOT); bilirubin, total; BUN; BUN:creatinine ratio; calcium, serum; carbon dioxide, total; chloride, serum; creatinine, serum; eGFR calculation; globulin, total; glucose, serum; potassium, serum; protein, total, serum; sodium, serum.

The drug screen analytes required in the urine drug test are amphetamine; barbiturate; benzodiazepines; cocaine or benzoylecgonine; fentanyl; methadone; opiates; oxycodone/oxymorphone; phencyclidine (PCP); propoxyphene; tramadol.

6 SAFETY CONSIDERATIONS

6.1 Known and Potential Risks to Participants

6.1.1 Collection of Blood

Collection of blood may cause slight discomfort, pain, bleeding or bruising at the collection site. Rarely, fainting or infection may occur. Only properly trained clinical staff will draw blood. The amount of blood collected is the minimal amount for proper analysis.

6.1.2 Internet-Based Data Collection

Data collection will be performed using the REDCap electronic data collection (EDC) and storage hosted by Johns Hopkins University. All data in REDCap will be de-identified. Each site will maintain a record of which participant corresponds to participant numbers assigned by REDCap. This file will be password protected if electronic or kept in a locked location if in the participant binder. Only authorized personnel requiring a password will be permitted to enter data. There is risk, although minimal, of unauthorized persons obtaining confidential information.

In brief, the REDCap Consortium consists of 84 institutional partners from CTSA, GCRC, RCMI and other institutions, in which JH is an active participant. It was developed by CTSA partners at Vanderbilt, with the goal of enabling investigator research through the establishment of a more user-friendly database system. This consortium supports two secure web-based applications designed to enable data capture for research studies. The software contains an intuitive interface for collecting data with data validation commands, allows for automated export procedures to statistical packages (e.g. SAS) and provides advanced features that allow for branching logic, file uploading, etc. The system itself is supported on MySQL, an open source database similar to SQL/Oracle, and operates on a web-based system. All servers are backed-up at each data center (institution) and include password protection to provide enhanced security while maintaining accessibility via the internet.

6.2 Complaints and Adverse Events

6.2.1 Data safety monitoring

This study implements on-label use of the medication GLE/PIB for persons with Hepatitis C Virus whose current infection has not been exposed to prior direct-acting antiviral (DAA) therapy. There are not expected to be changes to the known safety and efficacy data for this agent. Thus, there will be no formal data safety monitoring board. The site investigator will determine grade (Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events) and relatedness to GLE/PIB for all adverse events and if any serious unexpected adverse events arise, the site investigator will discuss and decide with the study Principal Investigator whether this protocol should be suspended.

6.2.2 Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal

laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

An AE can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol specific criteria (see Section 6.3 regarding toxicity management) and/or if the investigator considers them to be AEs.

Adverse event reporting will follow the requirements outlined below. Adverse events will also be recorded and tracked in a safety monitoring database by the investigators. Serious adverse events (SAEs) will be reported to the Institutional Review Board according to IRB guidelines and to AbbVie via the Johns Hopkins University Transplant Oncology and Infectious Diseases Clinical Research Center (TOID CRC).

All Grade 3 or higher and all SAEs related to the use of GLE/PIB in intervention arm or prescribed DAA course in SOC arm will be collected. Thus, AEs and SAEs will only be collected from the time of first DAA dose to 30 days after completion of DAA course.

All Grade 3 or higher AEs and all SAEs will be reviewed by the principal investigator as they occur in a timely manner. All AEs related or possibly related to GLE/PIB will be reported by the site to the TOID CRC within 72 hours of the site being made aware via the REDCap EDC system. All SAEs will be reported to the TOID CRC via the REDCap EDC system within 24 hours of the site being made aware. Notification of all SAEs will be made to AbbVie by the TOID CRC via email within 24 hours of entry into REDCap.

6.2.3 Adverse Event Relationship to Study Drug

For the purpose of medical management, all Grade 3 and 4 AEs and laboratory abnormalities that occur during the study must be evaluated by the Investigator. All AEs and laboratory abnormalities deemed "clinically significant" based on the medical judgment of the Investigator will be managed and followed to a satisfactory clinical resolution.

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Reasonable Possibility – After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.

No Reasonable Possibility – After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

6.2.4 Pregnancy

While not an AE, pregnancy in a study subject should be monitored. Information regarding a pregnancy occurring up to 30 days after end of treatment in a study subject and the outcome of the pregnancy will be collected.

In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the Treatment Period, the administration of study drug may be continued at the Principal Investigator's discretion after discussion with the subject, if the benefit of continuing study drug is felt to outweigh the potential risk. If a subject is discontinued, the subject will be monitored for SVR in the Post-Treatment Period.

6.3 Toxicity Management

The management of specific AEs and laboratory parameters is described below. This includes the following laboratory abnormalities:

If a subject experiences a post-baseline increase in alanine aminotransferase (ALT) to > 3 × upper limit of normal (ULN), which is also > 2 × baseline value, the subject, should have a confirmatory ALT measurement performed.

If, the ALT increase is confirmed to be > 3 × ULN, which is also > 2 × baseline value, the recommendations below, should be followed:

- Evaluate for alternate etiology of ALT elevation; document in the source, update the medical history and concomitant medications eCRF (if applicable), and obtain Anti-hepatitis A virus immunoglobulin M (HAV IgM), Anti-hepatitis A virus total (HAV Total), Anti-hepatitis B core (HBc) IgM, Anti-HBc Total, Anti-Hepatitis B surface (HBs), Hepatitis B Virus (HBV) DNA, HBsAg, Anti-hepatitis E virus immunoglobulin M (HEV IgM), Anti-hepatitis E virus immunoglobulin G (HEV IgG) and HEV RNA, and other additional tests, as appropriate.
- Manage the subject as medically appropriate.
- Repeat ALT, aspartate aminotransferase (AST), total and fractionated bilirubin, alkaline phosphatase and international normalized ratio (INR) within 1 week. Repeat liver chemistries as indicated until resolution.

Discontinue study drug if any of the following is observed at any time:

- ALT level is ≥ 3 × ULN and total bilirubin of > 2 x ULN without initial findings of cholestasis (elevated serum alkaline phosphatase) in the absence of an alternate etiology including another drug capable of causing the observed injury.
- Increasing direct bilirubin or INR or onset of symptoms/signs of hepatitis.
- At the discretion of the investigator.

Alternate management of ALT increases is permitted with approval of the Sponsor Medical Director.

6.4 Product Complaint

A Product Complaint is any complaint related to the biologic or drug component of the product.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, or packaging issues.

Product Complaints concerning the investigational product must be reported to the TOID CRC via the REDCap EDC system within 24 hours of the study site's knowledge of the event. Notification of product complaints will be made to AbbVie by the TOID CRC via email within 24 hours of the site reporting the complaint. Product Complaints occurring during the study will be followed up to a satisfactory conclusion.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The primary analysis for the effectiveness of the test and treat strategy versus standard of care referral for HCV treatment initiation will be assessed using a logistic regression model and a two-sided Type 1 error rate (alpha) of 0.05. Since participants will be recruited from drug treatment programs at which they are receiving ongoing treatment for substance use disorder, we expect low rates of lost to follow up (10%).

7.2 Definition for Analysis Populations

All analyses will be conducted with a modified intention to treat of approach, which excludes randomized participants who were found on testing to have an undetectable HCV RNA, HBsAg positive or a platelet count <150,000.

7.3 Statistical Analyses

7.3.1 Primary Analysis

Sample Size and Power Consideration Estimation

The planned sample size for the trial is 124 participants enrolled and randomized in a 1:1 ratio to test and treat strategy versus Standard of Care referral. This sample size is based on preliminary data from the CHAMPS study, which offered free onsite HCV treatment to HIV infected patients at an urban infectious disease clinic and achieved a 70% HCV treatment initiation rate.[15] Data from community-based sites including the AIDS linked to the intravenous experience study suggest an HCV treatment start rate of 30% among community based people who use drugs enrolled in the oral DAA era in Baltimore[21]. Given differences in HCV treatment policies and restrictions, HCV treatment rates were estimated to be up to 55% in other cities prior to the COVID-19 pandemic. HCV treatment uptake rates reduced during and post-COVID 19. We estimate HCV treatment uptake between 30-50% in different cities, averaging 40%. Using these data points as estimates for treatment initiation in the test and treat arm (70%) and the treatment uptake in the referral arm (40%) power calculations are as follows. With a total sample size of 124 participants, we have 85% power at an alpha of 0.05 to detect a statistically significant difference in treatment initiation in the test and treat strategy versus the standard referral arm. The sample size of 124 allows for 110 completers should there be a ~10% drop out rate. If there is no drop out then the total enrollment of the HCV infected participants will be 124. We continue to expect that the treatment uptake will be 70% with the proposed test and treat interventions. Our proposed sample size of 55 completers per group (62 per group including possible drop outs) is adequate to distinguish between the hypothesized 70% uptake and the 40% non-intervention arm uptake with 85% power at the p = 0.05 threshold.

7.3.2 Statistical analyses

All analyses will be conducted with a modified intention to treat of approach, which excludes randomized participants who were found on testing to have an undetectable HCV RNA, HBsAg positive or a platelet count <150,000. Our primary analysis will be logistic regression analyses. Statistical inference will use a two-sided Type 1 error rate of 0.05 and 95% confidence intervals.

7.3.3 Secondary outcomes

1) HCV treatment completion: Proportion of those initiating treatment who complete HCV treatment defined as taking more than 90% of prescribed treatment course by expected end of treatment date.

2) SVR 12: Proportion of participants with HCV RNA <15 IU/ml between 10 and 36 weeks after end of treatment in each randomization arm.

   Analysis for secondary outcomes 1 and 2 will be logistic regression analyses.

3) Time to HCV treatment initiation after randomization.

For secondary outcome 3, a time to event outcome, we will perform survival (Kaplan Meier) analysis for time to HCV treatment initiation.

Analysis of adverse event data will primarily be descriptive. Adverse event data will be compared between randomization arms using Fisher's exact Test.

7.3.4 Sensitivity analysis for missing data

We expect very low missingness of data in our results. We will explore the demographic and clinical characteristics comparing persons with full and incomplete follow-up, and try to define the mechanism of missingness with the input of study staff about clinical operations. This experiential input is necessary, because there is no data-driven mechanism to decide on non-ignorability of missing data. For Missing Not At Random sensitivity analysis, we will use multiple imputation methods to test the robustness of our results.

7.3.5 Qualitative analysis

Analysis. Transcripts of audio-recordings from in-depth interviews will be uploaded into MAXQDA software[22] for the purposes of coding and analysis. Our approach to the qualitative data will involve thematic analysis and employ both inductive and deductive coding techniques.[23,24] We will first develop an *a priori* code book that reflects key analytic dimensions of the RE-AIM framework. New themes that emerge from the data will be analyzed through a grounded theory approach, allowing for themes to emerge and ensuring that the knowledge assembled from the observational data is not subjected to the themes solely established through the in-depth interview guide. Qualitative analysis will proceed by first exploring broad patterns and experiences of patients, peers, drug treatment clinic leadership and staff, and then assessing possible similarities and differences in experiences between staff (including different ages, sex, and level of training) and the 5 different sites. Two coders will conduct open coding on three transcripts to develop initial coding schemes. After discussion and development of a combined draft scheme, two more interviews will be coded, and these will be further discussed and inform a final coding scheme which will be developed. Through weekly meetings, a team approach to data analysis will be employed, whereby different analysts provide feedback on emerging interpretations and check emerging categories against the raw data. In this way, an "audit trail" will be used to help ensure trustworthiness of findings, gather input from multiple perspectives, and enhance reliability.

Mixed methods. The qualitative data will provide context to the quantitative data and in-depth understanding of barriers and facilitators to program implementation in the local context. We will merge and integrate quantitative and qualitative data. The qualitative themes will be compared to survey results, combined and jointly displayed. We will create a matrix relating qualitative themes to quantitative variables. Findings will inform future programming efforts.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The JHM IRB will provide IRB oversight for all domestic sites. Expert review of the research protocol is carried through the work of the JHM IRB to ensure that research is well designed and likely to yield generalizable knowledge, and that risks are both commensurate with benefit and accurately disclosed to research participants. This protocol, the ICF, and any subsequent modifications will be reviewed and approved by the JHM IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the participant (or legal representative or person with power of attorney for participants who cannot consent for themselves). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject, or legal representative and this fact will be documented in the participant's record.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the Investigator are specified in Appendix D.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or codes.

8.4 Johns Hopkins University Transplant Oncology and Infectious Diseases Clinical Research Center (TOID CRC)

8.4.1 Protocol and Consent Version Control

The TOID CRC will maintain protocol and consent version control. The umbrella protocol will not be modified by any site other than the TOID CRC. All amendments and other pertinent protocol information are sent to the participating sites via email, as a PDF document, after approval by JHM IRB. The TOID CRC will maintain a Regulatory Database for this study that will record the protocol and informed consent version, JHM IRB approval and expiration date, participating site distribution date and confirmation of receipt via the Protocol Signature Page that will be signed and dated by the site's Principal Investigator and returned to the TOID CRC.

8.4.2 Data Collection and Management

Study data will be entered via eCRFs using the REDCap EDC system. The REDCap EDC is a secure web-based electronic data capture system. Each person entering data in the EDC system must complete a training. After verification of appropriate training, the Data Center will issue a unique username and password. The username and password will create an audit trail each time data is entered. Routine remote and/on-site monitoring will be conducted to verify timely and accurate entry of data.

8.4.3 Protocol Events and Deviations

Sites will report all SAEs to the TOID CRC by entering the SAE directly into REDCap. When the site enters a SAE into the study database, an automatic email will be generated and sent to the TOID CRC Safety Contact. The TOID CRC will then review the case to ensure completeness and clarity, and confirm seriousness and attribution. In addition, all sites will follow their local reporting requirements. Domestic sites will also be responsible for reporting protocol events and/or protocol deviations that meet JHM IRB prompt reporting directly to the JHM IRB:

https://www.hopkinsmedicine.org/institutional_review_board/guidelines_policies/organization_policies/prompt_reporting_policy.html

8.4.4 Annual Enrollment Data

Annual enrollment data will be directly reported to the JHM IRB by the TOID CRC.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH GCP, and applicable local regulatory requirement(s).

10 DATA QUALITY ASSURANCE

Sponsor will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The end-of-study is defined as the date of the last subject's last visit.

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APPENDIX A. SCHEDULE OF EVENTS (ALL PARTICIPANTS)

	Recruitment Screen	Day 0	Treatment Day 1	Treatment Week 4	End of Treatment -0d/+30d	Post-Treatment Week 12 -14d/+30d	Post-Treatment Week 24 -14d/+30d	Post-Treatment Week 36 -14d/+30d	Early D/C Visit
Eligibility Review[a]	X	X							
Vital Signs[b]		X							
Demographics		X							
Medical History		X							
Concomitant Medications[c]		X			X				
Randomization		X							
Referral to HCV Treatment (SOC Arm Only)		X							
AE/SAE Collection[d]			→	→	→				
Laboratory Testing									
HBsAg		X							
Pregnancy Test[e]		X							
CBC[f]		X							
HCV RNA[g]		X			X	X		X	X
CMP		X			X	X			X
Urine Toxicology Screen		X			X	X	X	X	
Dried Blood Spot		X			X	X	X	X	X
Surveys/Questionnaires									
Study Survey		X			X	X	X	X	
PRO/QOL Measures		X			X	X	X	X	
Intervention Arm Only									
Peer Contact[h]		X	→	→	→	→			X
Study Drug Dispensation[i]			X	X					

[a]Including documentation of HCV infection (antibody) and treatment history.
[b]Including height, weight, temperature, pulse, respiratory rate, and blood pressure.
[c]All medication (including supplements and over-the-counter) will be collected.
[d]AE/SAE collection starts with initiation of DAAs, continues through 30 days after last DAA dose.
[e]For all participants of childbearing potential. Urine or serum test.
[f]With or without differential.
[g]CLIA certified.
[h]Peer contact to occur weekly and as needed between visits until SVR 12. Contact can be in-person, via phone, or video.
[i]Study drug can be dispensed in smaller amounts more frequently if participant is unable to maintain 4-week supply at home.

APPENDIX B. SCHEDULE OF EVENTS (PARTICIPANTS WHO DO NOT START HCV TREATMENT BY WEEK 12 AFTER RANDOMIZATION IN EITHER ARM)

For participants who have not initiated treatment by Week 12 after randomization, complete the following.

	Week 12 after randomization -14d/+30d	**Week 24 after randomization** -14d/+30d	**Week 36 after randomization** -14d/+30d	**Week 56 after randomization** -14d/+30d
Laboratory Testing				
Urine Toxicology Screen	X	X	X	X
Dried Blood Spot	X	X	X	X
HCV RNA[e]		X		X
Surveys/Questionnaires				
Study Survey	X	X	X	X
PRO/QOL Measures	X	X	X	X
Rescreen for SOC Participants to Rollover to Intervention Arm				
Eligibility Review		X		
Vital Signs[a]		X		
Concomitant Medications[b]		X		
HBsAg		X		
Pregnancy Test[c]		X		
CBC[d]		X		
CMP		X		
Peer Contact[f]		→		

[a]Including height, weight, temperature, pulse, respiratory rate, and blood pressure.
[b]All medication (including supplements and over-the-counter) will be collected.
[c]For all participants of childbearing potential. Urine or serum test.
[d]With or without differential.
[e]CLIA certified.
[f]Participant will meet with peer on date of rescreen. If participant is still eligible for rollover to Intervention Arm after rescreening labs result, peer contact to occur weekly and as needed between visits until SVR 12. Contact can be in-person, via phone, or video.

APPENDIX C. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
ALT	Alanine aminotransferase
ART	Anti-retroviral treatment
AST	Aspartate aminotransferase
CBC	Complete blood count
CMP	Comprehensive metabolic panel
DAA	Direct-acting antiviral agent
DAIDS	Division of AIDS
D/C	Discontinuation
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
eCRF	Electronic case report form
EDC	Electronic Data Collection
GCP	Good Clinical Practice
GLE	Glecaprevir
HAV	Hepatitis A virus
HAV IgM	Hepatitis A virus immunoglobulin M
HBc	Hepatitis B core
HBs	Hepatitis B surface
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HEV IgG	Hepatitis E virus immunoglobulin G
HEV IgM	Hepatitis E virus immunoglobulin M
HIV	Human immunodeficiency virus

ICF	Informed consent form
ICH	International Conference for Harmonization
IDI	In-depth interview
IDSA	Infectious Diseases Society of America
IEC	Independent ethics committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International normalized ratio
IRB	Institutional Review Board
IU	International units
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
mL	Milliliter
OTP	Opioid treatment program
PIB	Pibrentasvir
PRO	Patient Reported Outcomes
PWUD	People who use drugs
QOL	Quality of life
RE-AIM	Reach, Effectiveness, Adoption, Implementation, and Maintenance framework
RNA	Ribonucleic acid
SAE	Serious adverse event
SOC	Standard of care
SUD	Substance use disorder
SVR 12	Sustained virologic response 12 weeks post dosing
ULN	Upper limit of normal
WHO	World Health Organization
WOCBP	Woman of childbearing potential

APPENDIX D. RESPONSIBILITIES OF THE INVESTIGATOR

Clinical research studies sponsored by AbbVie are subject to the International Conference for Harmonisation (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and **Operations Manual**, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date
Name of Principal Investigator (printed or typed)	

APPENDIX E. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0 Initial version.	**19-FEB-2021**
Version 2.0 Removed washout period of some prohibited medications from eligibility criteria. Added language specifying research labs to be conducted.	**12-APR-2021**
Version 3.0 Removed rollover to Appendix A Schedule of Events for participants who initiate HCV treatment after Week 12 post-randomization.	**22-JUL-2021**
Version 4.0 Updated study sites. Clarified secondary endpoints. Clarified study definition of 6 months. Clarified that study screening labs can happen prior to randomization. Clarified study definition of prior HCV treatment. Added timing for participant IDI. Added information for determining participant is lost to follow up. Updated urine toxicology testing requirements. Expanded study visit windows. Added Week 56 visit for participants who do not start HCV treatment by Week 12.	**08-MAR-2022**
Version 5.1 Updated sample size from 250 to 124. Added language to primary analysis section to clarify updated sample size. Updated primary analysis section to reflect modification of a statistical calculation.	**14-DEC-2022**