HCV ST&RT

A randomized study of a rapid HCV treatment initiation strategy (HCV Seek, Test and Rapid Treatment – HCV ST&RT) compared to standard care in young PWID

A single center randomized controlled trial

Investigator-initiated and funded by Gilead Sciences ISR

PROTOCOL AMENDMENT 1

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0.0 Amendment Information

0.1 Rationale for the Amendment:

The initial protocol proposes a randomized controlled trial of rapid-start hepatitis C (HCV) treatment intervention co-located at a syringe service program. Due to the impact of the COVID-19 pandemic in New York City, enrollment in this protocol has been temporarily suspended. As New York starts to plan recovery from COVID, it is likely that elements of service delivery for people who inject drugs (PWID) will be very different. Foremost, the impact of COVID-19 on syringe service programs may limit the ability to offer co-located interventions. A recent national survey showed that 43% of programs have reduced services and nearly all had eliminated HCV and HIV testing due to the need for person-to-person contact.[1] The prospect of an economic downturn may further limit the ability of these programs to provide health services in a tighter funding environment.

In the meantime, the need to adapt to the pandemic has rapidly increased the use of telemedicine services to engage with patients without physical contact.[2] It is not clear whether telemedicine is equitably accessible across different patient populations.[3] Telemedicine has been found to be acceptable for hepatitis C management in patients in several healthcare settings.[4,5] Our intervention serves a unique population not covered by prior studies: they are currently injecting and recruited from the community, and so may face significant healthcare access barriers. On the other hand, they are a young population (<30 years old) that may be technologically equipped to embrace telemedicine-based HCV treatment. Understanding how to adapt existing community-based healthcare intervention for populations with limited healthcare access will be critical in the post-COVID era.

In this amendment, we will change the enrollment and analysis plans of our randomized study (called part A). This will involve conducting the analysis and reporting of comparative data between intervention and control arms, with the same study endpoints as the initial proposal. The main reason for ending enrollment at this time is the long delay we are likely to face before a co-located intervention can be offered in a physical syringe service program space. Instead, we will adapt our intervention to be telemedicine-based for continued enrollment into a nonrandomized treatment group (Part B). After the end of follow-up for part B, we will describe outcomes and compare to the previously randomized control population, to test if telemedicine-based engagement is feasible, safe, and noninferior to the co-located intervention.

0.2 Protocol Changes:

1. **Section 1.2**

Change: Addition of: In Part B, all participants will be enrolled to the intervention group, modified to allow telemedicine delivery.

2. **Section 1.4:** Intervention Arm

Change: For participants entering in Part B, the co-located rapid start intervention will be converted to telemedicine rapid-start intervention. Consented participants will have same-day or next-day telemedicine visits with a hepatitis C provider and baseline blood testing will be arranged on a personalized basis utilizing convenient community-based laboratory facilities (including current co-located SSP and commercial laboratories). For participants found to be HCV PCR positive, personal delivery or pick-up of a 28-day supply of sofosbuvir/velpatasvir (Epclusa ®) will be

arranged. Telemedicine visits will be arranged two weeks after treatment delivery. For participants who confirm treatment initiation, side effects will be assessed, delivery/pick-up of the final 56-day of medication will be arranged, and week 4 monitoring labs will be offered (no longer required) and arranged.

3. **Section 1.7:** Secondary Objectives

Change: To assess the feasibility, safety, and effectiveness of a telemedicine-based rapid start intervention for hepatitis C treatment in young people who inject drugs.

4. **Section 3:** Study Design

Change: For participants entering in Part B, randomization will not occur. All participants will be assigned to the intervention arm, which we will call the telemedicine arm in this document.
Rationale: The part B telemedicine arm will not be randomized, and instead will be compared to previously randomized arms. This is in order to maximize sample size exposed to the intervention with the available remaining budget and grant period.

5. **Section 4 :** Participant Selection and Enrollment

Change: For participants entering in Part B, enrollment may occur in person or remotely (no person-to-person contact needed)
Rationale: Remote enrollment procedures will allow continued referral and enrollment even without the physical location of the syringe service program. Informed consent will be converted to electronic informed consent using a RedCAP survey, a procedure we have successfully implemented at Weill Cornell for COVID-related studies.

6. **Section 5.1** : Schedule of Study Events

Change: Week 4 and Week 8 laboratory draws are now changed to optional, to minimize travel and physical contact. Monitoring labs for re-infection have been eliminated, and re-infection will not be analyzed for the telemedicine cohort. Instead, individuals will reach the study endpoint at either SVR 12 or at week 48, whichever comes first. The frequency of medical visits will be unchanged but physical exams will no longer be performed except as possible through telemedicine. Weekly telephone or video check-ins will also continue.

7. **Section 5.8**: Storage of samples for future analysis

Change: Storage samples collected only when feasible for Part B.
Rationale: Since we will now be utilizing clinical laboratories, storage of samples for research purposes will occur when feasible, but not required for all participants and all timepoints.

8. **Section 8.1** Sample size

Change: Data on the randomized controlled portion of the study (Part A) will be analyzed based on enrollment through March 1, 2020 so the power to detect a difference between the 2 groups will be reduced from what was calculated for a sample size of 54 patients..
Rationale: The COVID pandemic created a natural break in enrollment and inability to continue study as planned.

9. **Section 8:** Statistical and Analytic Considerations

Change: Adding the Part B analysis for comparing the telemedicine arm to the previously enrolled study arms.
Rationale for change: We will compare the proportion of patients who achieve SVR12 in each Part B telemedicine to (1)Part A intervention (2) Part A control, using Chi-square or Fishers' exact testing, using an intention-to-treat approach in which participants are analyzed in the group to which they are randomized. Participants with negative confirmatory HCV RNA PCR tests on study entry will not be included in the analysis, consistent with our existing approach.

10. **Consent form**:

The consent form was revised to reflect the addition of Part B. Part A participants do not need to be reconsented.

1.0 Synopsis

1.1 Purpose of Study:

The purpose of this randomized study is to determine whether a community-based test and treat model of hepatitis C (HCV) care delivery will be superior to the usual care practice of referral to specialist clinics for the outcomes of sustained virologic response at 12 weeks after treatment and initiation of HCV treatment for persons who inject drugs (PWID) between ages 18 and 29 who are naïve to HCV treatment

1.2 Design:

ST&RT is a randomized open-label clinical trial conducted in two parts. In part A, which HCV infected PWID between ages 18 and 29 will be randomized to either receive the same-day treatment initiation of the FDA-approved fixed dose combination of sofosbuvir 400mg and velpatasvir 100mg (SOF/VEL) with follow up and medical monitoring at a community site (Intervention arm) or to receive referral to an HCV treatment provider's office (Usual Care Arm). In Part B, participants will be enrolled to receive hepatitis C rapid treatment initiation in a telemedicine model.

1.3 Participant selection:

1.3.1 Inclusion Criteria

Persons are eligible for study inclusion if they: (a) are HCV antibody positive, (b) are 18 to 29 years of age, (c) have injected drugs in the past 30 days, (d) are HCV treatment naïve, (e) are English speaking

1.3.2 Exclusion Criteria

Persons excluded from the study will be (a) HIV coinfected persons (b) pregnant women, or women planning on becoming pregnant (c) participants with end-stage renal disease (d) participants with decompensated cirrhosis (c) participants on medications with treatment limiting interactions with SOF/VEL (detailed below). In part B only, participants who cannot participate in telemedicine visits (lack of telephone, smart phone or computer or internet connection) will be excluded.

1.4 Study procedures

1.4.1 Enrollment and sampling

Potential research participants will be recruited by referral from an ongoing NIH funded study aiming at preventing HCV among young current injectors (R01DA041501), hereafter referred to as the parent

study. The parent study will conduct a randomized, controlled trial to assess the effectiveness of a "Staying Safe" prevention intervention in reducing injection-related risk behavior and HCV incidence among 18-29 year-olds who inject opioids (heroin and/or POs) and test HCV and HIV antibody-negative at screening. The parent study is continuing to enroll participants and perform HCV testing. Whereas previous procedures would have required that the participant be referred physically to the syringe service program, we are now allowing for remote enrollment by phone or video as the first point of contact. Since the parent study is still operating, we expect to continue to receive referrals of HCV-infected people. Candidates for the parent study who test HCV antibody positive at the screening visit, will be immediately offered enrollment in ST&RT. The target sample size of 27 participants per arm is selected to show a hypothesized difference in SVR12 rates of about 35% with 80% power at a level of 0.05. Participants who are enrolled but negative on confirmatory testing (an expected 25% of participants) will be replaced. These participants will not receive treatment interventions but continue to be followed for monitoring of HCV re-infection incidence. We anticipate enrolling 36 participants per arm to achieve the target of 27 confirmed infections per arm.

1.4.2 Intervention Arm

In Part A: Participants randomized to the intervention arm will have a same-day visit with a study physician. Those who are interested in being treated for their HCV, and have no contraindication, will (a) have standard of care baseline laboratory testing drawn and be given a one-week 'Starter-Pack' (7 day supply) of sofosbuvir 400mg/velpatasvir 100mg. Subsequent supplies of DAA therapy will be distributed to HCV RNA test positive participants as one 21-day and one 56 day supply to complete a 12-week treatment course. Those participants with negative confirmatory HCV RNA testing will be contacted via telephone and instructed not to begin the medication, and will not be given additional medication supplies.

Participants will be contacted weekly while receiving sofosbuvir/velpatasvir by text message to assess adherence, potential adverse effects, and offered other tele-support as needed. Scheduled study visits will occur at 4 weeks, upon treatment completion or discontinuation (study week 12), study week 16 (corresponding to SVR4), study week 24 (corresponding to SVR12), study week 36, and study week 48. Each study visit will consist of laboratory testing, semi-structured interview, and physician visit. Additional medical visits may be scheduled at the participants' request. Additionally, each participant will be scheduled for a one-time counseling session for prevention of reinfection during their course of treatment. Referral to harm reduction and/or opioid substitution treatment programs will be provided for interested participants, but utilization of these services is not a condition of enrollment in the study or of HCV treatment provision.

In Part B: Participants will be enrolled in the telelmedicine arm, and will have a same-day or next-day telemedicine visit with the hepatitis C provider. Initial evaluation will be either via telephone, video, or in-person at the syringe service program depending on patient preference. Blood testing will be arranged at local community laboratory facilities. Participants with positive HCV RNA will have delivery of a 28 day supply of sofosbuvir/velpatasvir, and a 56 day supply after completion. Weekly check-ins will occur by phone, and participants will have clinical laboratory monitoring at week 4 (optional), week 12, every 12 weeks thereafter until completion of follow up. Participants will complete a short structured survey at weeks 0, 12, 24, 36, and 48, also over video or telephone.

1.4.3 Usual Care Arm

During Part A: Participants randomized to the usual care arm will have a same-day lab draw for confirmatory HCV RNA testing. Those who test RNA positive will be referred to local clinic or community based HCV medical providers.

Participants will be contacted monthly via telephone for a short questionnaire. Scheduled study visits will occur at study weeks 12, 24, 36 and 48 for semi-structured interviews and HCV RNA testing.

During Part B: no participants will be assigned to the usual care arm

1.5 Hypothesis

We hypothesize that the ST&RT intervention will be accepted by HCV infected PWID aged 18-29, and lead to higher rates of treatment initiation, completion and SVR12 compared to the usual practice of referral to community HCV providers.

1.6 Primary Outcome

The proportion of participants who achieve sustained virologic response defined as an undetectable HCV RNA viral load 12 weeks after the cessation of treatment (SVR12), in the intervention arm compared to the usual care arm by study week 48.

1.7 Secondary Outcomes

1. The proportion of participants who initiate treatment for HCV in the intervention arm compared to the usual care arm by study week 48.

2. The proportion of participants who complete the prescribed course of treatment for HCV in the intervention arm compared to the usual care arm by study week 48.3. The proportion of participants after initiating HCV treatment did not complete it compared to the usual care arm by study week 48.

4. The proportion of participants in both arms who achieve SVR 12, or are RNA negative at baseline, that have HCV reinfection (defined in section 5.5) by study week 48.

5. To characterize the HCV genotype and presence of resistance associated substitutions (RAS) in those treated patients with HCV reinfection or relapse.

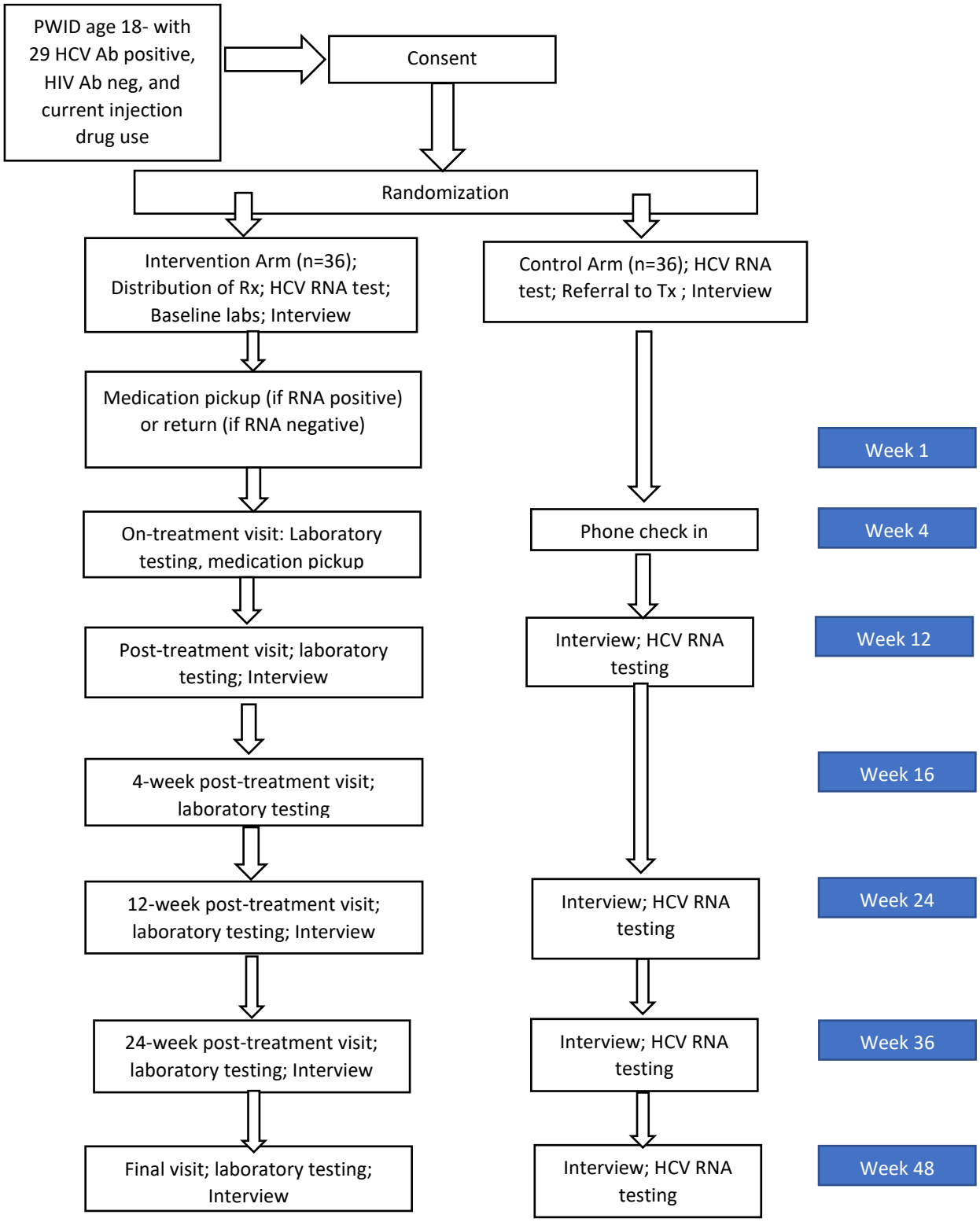
6. To examine impact of engagement in HCV treatment on substance use behaviors and injection risk.

7. Qualitative assessment using semi-structured interviews to evaluate the acceptability of the intervention versus usual care, the barriers to initiate and complete treatment, and factors influencing successful treatment outcomes

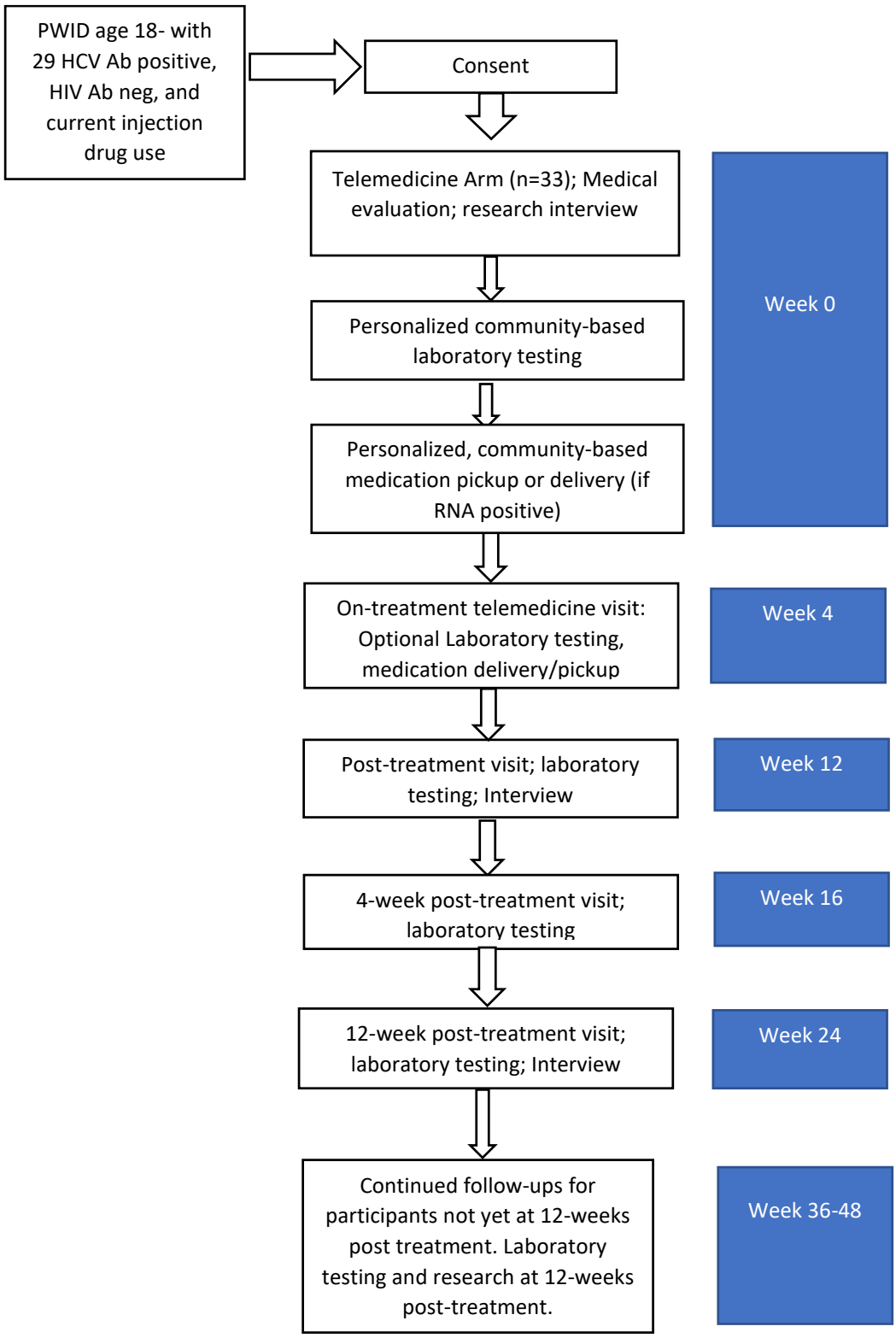
8. To assess the feasibility, safety, and effectiveness of a tele-medicine based rapid start intervention for hepatitis C treatment in young people who inject drugs.

1.8 Schematic

1.8.1: Part A Schematic



1.8.2: Part B Schematic



2.0 Introduction

2.1 Background

Our proposed pilot study will examine the effectiveness and acceptability of a novel rapid) treatment initiation strategy that if found effective could be further studied as part of a new model for HCV treatment delivery in young PWID, namely: Seek, Test and Rapid Treat (HCV ST&RT, a modification of the well-known Seek, Test and Treat model for HIV). This strategy has potential to avoid the attrition observed on the HCV care cascade and reach the population most important for treatment as prevention, young PWID. This study focuses on Rapid Treatment initiation and will not study the Seek and Test components, however we will refer to the strategy as HCV ST&RT throughout this proposal for simplicity.

The United States has been experiencing a dramatic opioid epidemic among young people for over a decade. Between 2002 and 2013, heroin use in the United States has increased by 63%, with the largest increase (109%) in individuals aged 18-25.[6] The rise in injection drug use has been accompanied by increases in incident HCV infection.[7] Cases of acute HCV increased more than 2.5-fold from 2010-2014 with the greatest increases among people age 20-29.[8] Recent HCV outbreaks across several states reflect the widespread transmission of HCV in PWID,[9-14] and modeling studies indicate that counties with higher rates of drug overdose deaths and prescription opioid sales are vulnerable to HCV outbreaks in the future.[15]

The recent development of direct acting antivirals (DAAs) with high efficacy and tolerability has revolutionized treatment of HCV.[16,17] Despite this, PWID are faced with multiple barriers to successful treatment: in addition to the effects of substance use and its comorbid conditions, PWID face mistrust within the medical system, explicit sobriety requirements from insurers, and a lengthy prior authorization process which necessitates extensive medical workup before initiating treatment.[18-20] Indeed, data from New York City suggest that only 38% of HCV-diagnosed PWID are engaged in care, and only 12% have initiated treatment.[21] Engaging and treating HCV in young PWID is further complicated by the common reluctance of this population to prioritize an infection that is unlikely to affect them for more than a decade.[22]

Overcoming the barriers to treat young PWID is essential: DAA therapy has the potential to impact the HCV epidemic, and among young PWID, it has the potential to prevent incidence, reduce prevalence, and potentially eradicate HCV infections entirely.[23-26] However, modelling studies on HCV prevalence show that in order to achieve elimination of HCV, extensive treatment scale-up is needed among PWID, the group at highest risk of transmitting disease.[26-29] The concept of treatment-as-prevention to control communicable disease is a cornerstone of public health for a number of diseases, including tuberculosis, sexually transmitted infections, and most recently HIV.[30] In fact, the demonstration of this concept helped to change the paradigm of HIV treatment, supporting early initiation of treatment before CD4 count reductions.

Rapid initiation of therapy in individuals at high risk of transmitting disease can help to minimize transmission. In a San Francisco study of HIV, the same-day initiation of antiretroviral therapy led to significantly faster time to viral suppression without sacrificing effectiveness.[31] This outcome was accomplished using an intervention consisting of (a) same-day access to an HIV provider, (b) accelerated insurance approval process (c) pre-approved regimens (d) 5-day starter packs, (e) observed administration of first dose, and (f) telephone follow-up. A similar model is now being implemented in sexually transmitted infection clinics in New York City (JUMPSTART program). In contrast to HIV where

there is an added challenge of retaining patients in care, the curable nature of HCV would appear to make it even more amenable to a Rapid Treatment Strategy.

In the past, a rapid treatment initiation approach would not have been possible for HCV. Interferon based therapies came with high toxicity, the need for supervised injection, and extensive medical monitoring. The advent of DAAs have allowed for increased decentralization of HCV management and treatment: tele-consultation with specialists is allowing treatment prescriptions by primary care physicians,[32] and the ease of DAA therapy can facilitate treatment to be located at community sites rather than in specialty clinics.[33,34] Our group, among others, has demonstrated the safety and effectiveness of medical evaluation and treatment with DAAs located at a syringe services program (SSP) in New York City, with sustained virologic response at 12 weeks (SVR12) of 85%.[35], and low rates of re-infection [unpublished data]. We are now studying this model on a larger scale in a randomized control trial comparing accessible SSP-based care with standard of care (R01 DA041298). However, our experience suggests that accessible care may not be sufficient incentive for young PWID to seek HCV treatment. This is especially true for suburban, housed, young PWID who are less likely to frequent existing harm reduction services than their older counterparts. To truly impact the prevalence and incidence of HCV, models of HCV treatment delivery and prevention need to focus on young, active PWID (where ongoing transmission is most concentrated).

Evidence suggests that high rates of HCV treatment engagement of young PWID is not possible without aggressively addressing the various barriers complicating the treatment cascade, specifically the delay between HCV confirmation and treatment initiation that currently results not only from the need for linkage to an HCV provider but also from (a) extensive pre-treatment lab testing (genotype, fibrosis assessment, and resistant testing) and (b) lengthy insurance prior authorization process.

Our proposed pilot study will examine the acceptability of HCV Seek, Test and Rapid Treatment (HCV ST&RT) and the effectiveness of Rapid Treatment Initiation in young PWID involving (1) immediate initiation of DAA treatment at time of diagnosis using starter packs, (2) community based treatment location, and (3) minimal in-person monitoring with text message-based support during the treatment process. We will achieve this using DAA treatment with a pan-genotypic treatment regimen, leveraging our existing community partnerships with local SSPs, and using mobile health technology to communicate with participants without necessitating frequent office visits.

2.2 Rationale for Study Design

2.2.1 Participant selection

Young PWID face significant challenges engaging with traditional medical care, due to a combination of factors. Mutual mistrust within the medical system works against engagement with a traditional, office-based healthcare status. Desire for confidentiality regarding drug use behaviors, especially among those using parental health insurance, may prevent engagement in care. A decreased perception of risk from HCV, which has a long latency period, may prevent young adults from prioritizing care for this disease. While perceived barriers to receiving treatment are high, and the perceived individual benefit is low, there is likely to be a significant societal benefit to treating this population due to the potential to prevent transmission among injection networks. HIV co-infected individuals are being excluded, because unlike their HIV-uninfected counterparts, significantly more monitoring and engagement than can be offered in our study will be needed for this population to address their HIV disease.

2.2.2 Treatment regimens used

The ability to provide same-day treatment is only feasible because of the introduction of pangenotypic antiviral regimens in which drug selection and dosing are identical for every HCV genotype and regardless of severity of liver disease. We have chosen one such regimen, sofosbuvir/velpatasvir, as our drug of choice for this study.

2.2.3 Schedule of follow up and monitoring

In keeping with the overall purpose of the intervention, medical visits will be limited to only those that are necessary for successful treatment. Current 12-week regimens are well-tolerated with minimal toxicity in most patients. At enrollment, HCV RNA PCR, chemistry, liver enzymes, blood count, HIV status, HBV status, and a test for liver fibrosis (imaging or laboratory), and a pregnancy test (for female patients) will be ordered. HCV RNA positive patients in the intervention arm will be asked to start medications after results of laboratory testing are reviewed. After medication start, one laboratory visit will be scheduled at 4 weeks to monitor liver enzymes and assess for on-treatment response via HCV PCR. Subsequently, liver enzymes and HCV PCR will be drawn at the end of treatment and 12 weeks of follow up to confirm response and cure. The purpose of the final monitoring visit will be to assess for HCV reinfection. Additional testing may be done if deemed necessary by clinical staff or to follow-up on abnormal results. Apart from the 4 study visits, the participants will each be contacted at least monthly by secure text message or phone call, and additional visits scheduled only if requested by the participant or deemed necessary by clinical staff. Participants randomized to the control arm, and HCV-negative participants in the intervention arm, will have text message or phone check in every month to determine their HCV treatment status., and study visits every 12 weeks for questionnaire, interview, and HCV RNA testing.

2.2.4 Outcome selection

The primary outcome of SVR12 is selected as a binary measure, due its use as a surrogate marker for HCV cure. Secondary outcomes will assess movements of participants along the HCV treatment continuum, and allow for identification of participants who were lost to follow up during treatment, a potentially important outcome in this population. There is concern that a participation of current PWID may be subject to reinfection after cure, and we will assess for this by repeating HCV RNA at 48 weeks. While longer follow-up for reinfection would be valuable, we do not feel it is feasible in the current study. Finally, to assess the acceptability of this intervention, examine its impact on substance use behaviors and injection risk, and to refine future iterations, we will solicit participant outcomes via survey and interview.

2.3 Summary of Risks and Benefits

Potential risks of the study include:

- Breach of confidentiality regarding drug use behaviors and hepatitis C disease status
- Adverse events from HCV treatment
- Adverse events from study related laboratory and imaging tests
- In the event of treatment failure, there is a risk of resistance developing to the treatment regimen
- Emotional distress from survey and interview questions pertaining to sensitive topics including mental illness, sexual health, and substance use behaviors.

Potential benefits of the study include:

- In the intervention arm, easily accessible HCV treatment that bypasses insurance authorization procedures and associated benefits of HCV cure
- Linkage to harm reduction services for PWID, with facilitated referral to substance use treatment if interested
- Public health benefit of HCV treatment in PWID, in terms of theoretical reduction in transmission potential.
- Financial compensation for participation in study procedures

3.0 Study Design

This is a single-center, open-label, randomized controlled trial, in which 72 HCV antibody positive participants between ages 18-29 will be recruited in two parts. During Part A, participants will be randomized to either the rapid treatment intervention arm, or the usual care control arm. During Part B, participants will be enrolled to the telemedicine arm. Recruited individuals must have used injection drugs in the past 30 days, have no medical contraindication to sofosbuvir and velpatasvir treatment, be HIV uninfected, and be HCV treatment naïve. During part B, they must have access to technology that allows telemedicine interventions (eg telephone, smartphone, or internet connection).

The goal of the study is to provide same-day, easily accessed medical evaluation and treatment to the intervention arm. During part A, participants randomized to the intervention will receive medical evaluation, laboratory assessment including confirmatory HCV RNA testing, baseline questionnaire/interview, and distribution of a 7-day medication "starter pack" on the day of enrollment. Participants who are HCV RNA negative will be notified by phone call, be asked to return their medications but continue to be followed for research visits every 12 weeks, similar to the control-arm. During part B, participants will have the option of an in-person evaluation at the syringe service program or a telemedicine visit on the day of enrollment or the following day. They will receive community based laboratory testing at a location that is convenient to them, and participate in study interview.

During part A, HCV RNA positive participants in the intervention arm will be asked to start medications, and return to pick up an additional 21-day supply. They will receive weekly text messages during treatment to record adherence. They will receive one follow-up medical visit at 4 weeks with laboratory evaluation, with distribution of the remainder of medications, and another visit at the end of treatment. One of these two visits (the participants' choice) will include counseling for prevention of reinfection. They will then have HCV RNA PCR testing at end of treatment and 12 weeks post treatment, and at 48 weeks to assess for reinfection. Each study visit will include a brief questionnaire and qualitative interview.

Participants in the control arm will be provided facilitated referral to community HCV providers by an on-site care coordinator already facilitating care at the community site. HCV RNA negative participants will be called to inform them of these results, and then discontinued from the study. HCV RNA positive participants will be asked during the semi-structured interviews as at 12, 24, 36 and 48 week if they engaged in HCV treatment to assess whether their HCV referral has been filled, and to record their current HCV treatment status. They will also receive repeat HCV RNA testing at week 12, 24, and 48. Participants that have started treatment will be asked to sign consent for release of medical records pertaining to HCV-related laboratory testing to determine achievement of treatment response.

During part B, HCV RNA positive participants will have a 28-day supply of medications delivered, or available for pickup, as they prefer. The schedule of visits will be similar except that laboratory testing at week 4 will be optional, and all visits will be offered through telemedicine.

The three arms will be compared for the main outcome of SVR12 using a modified intention to treat analysis in which participants will be analyzed in the group they are randomized except for those who are (a) discontinued due to HCV RNA negative status or (b) found to have previously undiagnosed HIV at enrollment. Secondary outcomes will be compared using the same modified intention to treat design.

4. Participant Selection and Enrollment

Participants will be recruited by referral from an ongoing NIH funded study. The parent study aims to prevent HCV among young current PWID (R01DA041501). Potential enrollees for the parent study will receive baseline HCV antibody testing, and those that test positive will be referred to ST&RT. Participants willing to enroll may be offered a same-day or next business day visit to assess for eligibility. If eligible for ST&RT, participants will receive informed consent. Ineligible participants may be offered enrollment into other ongoing studies. We do not expect to enroll participants from other referral sources for this study; however, participants meeting the inclusion criteria from other sources will also be considered if otherwise eligible For participants enrolling in part B, enrollment may occur in person or remotely (i.e. without person to person contact).

5 Study Procedures

5.1 Schedule of Events during Part A:

	Screening (performed by parent study	Entry		On-Treatment				Post-Treatment								Additional tests if Treatment interruption	Additional tests if Reinfection or Relapse
		Week 0		Week 4		Week 12		Week 16		Week 24		Week 36		Week 48			
Randomized Arm		Int.	Con.	Int.	Con.	Int.	Con.	Int	Con	Int.	Con.	Int.	Con.	Int.	Con.		
HCV Antibody	X																
Plasma HCV RNA PCR		X	X	X		X	X	X		X	X	X	X	X	X	X	
HIV-1/2 Antibody	X									X	X			X	X		
Hepatic Function Panel		X		X†		X†				X†				X†			
Hematology (CBCC)		X								X†							
Basic Metabolic Panel		X		X†													
Weight		X															
FIB-4 (calculated)		X															
Hepatitis B panel		X															
Pregnancy Test (female participants)		X		X*†		X*†											
HCV genotyping		X															X†
Physical Exam		X		X*†		X*†											
Adherence Assessment				Weekly for Int. arm†													

Reinfection Prevention counseling				Once for int. arm†													
Questionnaire and Interview		X	X			X	X			X	X	X	X	X	X		
Stored serum / plasma**		X	X			X	X	X		X	X	X		X	X		X

*If medically indicated

**In event phlebotomy is unavailable or unsuccessful, dried blood spots may be obtained by finger stick

† HCV RNA PCR Positive participants only

Windows: week 4 has a window of -7 days or + 14 days; Week 12 and 16 have a window of +7 days. Weeks 24 and 36 have a window of -14 to +28 days, and Week 48 has a window of -14 days.

5.2 Schedule of Events during Part B:

	Screening (performed by parent study	Entry	On-Treatment		Post-Treatment				Additional tests if Treatment interruption	Additional tests if Reinfection or Relapse
		Week 0	Week 4	Week 12	Week 16	Week 24	Week 36	Week 48		
Arm		Tel.	Tel.	Tel.	Tel.	Tel.	Tel.	Tel.		
HCV Antibody	X									
Plasma HCV RNA PCR		X	X‡	X	X‡	X	X	X	X	
HIV-1/2 Antibody	X					X		X		
Hepatic Function Panel		X	X†‡	X†		X†		X†		
Hematology (CBCC)		X				X†				
Basic Metabolic Panel		X	X†‡							
Weight		X								
FIB-4 (calculated)		X								
Hepatitis B panel		X								
Pregnancy Test (female participants)		X	X*†‡	X*†						
HCV genotyping		X								X†
Physical Exam		*	*	*						
Adherence Assessment			Weekly †							
Reinfection Prevention counseling			Once†							

Questionnaire and Interview		X		X		X	X	X		
Stored serum / plasma**		X‡		X‡	X‡	X‡	X‡	X‡		X‡

*If medically indicated

**In event phlebotomy is unavailable or unsuccessful, dried blood spots may be obtained by finger stick

† HCV RNA PCR Positive participants only

‡ Optional Lab draw

Windows: week 4 has a window of -7 days or + 14 days; Week 12 and 16 have a window of +7 days. Weeks 24 and 36 have a window of -14 to +28 days, and Week 48 has a window of -14 days.

5.2 Laboratory evaluations

5.2.1 HCV RNA PCR

HCV RNA PCR will be collected and performed at a clinical laboratory (Roche Diagnostics COBAS TaqMan). HCV RNA PCR will be performed for all participants at each study visit, regardless of randomized treatment arm.

5.2.2 HIV-1/2 Antibody

Participants referred to ST&RT will be required to have a positive HCV antibody and negative HIV antibody test prior to consent and randomization. On-site HIV testing will be offered prior to entry to participants who do not already have a documented negative antibody. HIV retesting will be every 6 months thereafter, in keeping with recommendations for individuals at ongoing risk for acquisition. As necessary, patients will be referred for additional HIV testing, including testing for acute retroviral infection using HIV-1 RNA PCR

5.2.3 FIB-4

The FIB-4 score will be calculated from laboratory testing using the following formula:[36]

$$\text{Fib-4} = \frac{\text{Age (years)} * \text{AST Level (U/L)}}{\text{Platelet count } (10^9/\text{L}) * \text{sq.rt.}(\text{ALT(U/L)})}$$

With a score of >3.25 representing advanced fibrosis.

5.2.4 Hepatitis B Panel

HBV testing will consist of HBV surface antigen, HBV surface antibody, HBV core antibody, HBV envelope antibody. HBV testing will be performed on all intervention participants at study entry.

5.2.5 Pregnancy Test

Serum beta-HCG will be performed for pregnancy test at study entry for all female participants, and may be performed again if there is concern for pregnancy. Participants of childbearing age will be provided contraceptive counseling, iterating the importance of contraception while on study medications.

5.3 Adherence Assessment

Adherence will be assessed for intervention group patients while on treatment. This will be accomplished by weekly secure text messaging consisting of a single item question.[37]

5.4 Qualitative and Questionnaire Evaluation

In-person interviews will be conducted for a sample of participants at the end of therapy (week 12), and at week 24, and 48. Participants will be asked to identify factors that promote or hinder engagement in HCV treatment, harm reduction services or substance use treatment. We will also inquire about participants substance use, sexual, and injection risk behaviors pre-, during and post- treatment. Participants who refuse interview will still be offered the HCV treatment. At the end of therapy, participants will be asked about changes in these factors, about uptake of safer injecting practices, engagement in harm reduction or substance use treatment, and the acceptability of the Seek, Test, and Rapid Treatment intervention.

5.5 Monitoring for reinfection

Participants in the intervention arm who receive treatment will have two post-treatment HCV RNA PCR tests, at 24 and 48 weeks, to monitor for re-infection after treatment completion. Participants who did

not receive treatment, either because of HCV-negative status or because of other reasons, will have HCV RNA PCR testing at 24 and 48 weeks. All participants in the control arm, regardless of HCV RNA status, will have HCV RNA PCR testing at 24 and 48 weeks, but it is expected that these may not be "post-treatment," as we expect treatment initiation to be delayed for the control participants.

True reinfection will be defined as a positive HCV RNA PCR with a different HCV genotype, occurring anytime after a documented SVR 12 (negative HCV RNA PCR 12 weeks or more after treatment completion).

Participants who (1) did not have a documented SVR 12 but did have a documented end-of-treatment response or SVR 4, and subsequently have a positive HCV RNA PCR OR (2) have a positive HCV RNA PCR after documented SVR12 with the same genotype as the initial infection, will be classified as possible reinfections. These participants will then be reclassified as either true reinfections or relapses based on viral sequencing of their baseline HCV infection compared to subsequent positive HCV RNA PCRs.[38]

5.6 Monitoring for incident HCV infection

Participants who had a negative HCV RNA PCR at baseline (or whose HCV RNA PCR became negative without treatment), who subsequently have a positive HCV RNA PCR will be considered incident HCV infections, but not reinfections.

5.7 Reinfection Prevention Counseling

All HCV RNA positive participants in the intervention arm will be scheduled for a harm reduction counseling session focusing specifically on HCV reinfection prevention. Participants will receive a condensed version of Staying Safe (Ssafe). Ssafe is an innovative, strengths-based, socio-behavioral HCV prevention intervention for young PWID. Ssafe addresses multi-level "upstream" determinants of risk that occur relatively early in the causal chain of risk, including eco-social conditions, social relations and risk situations, in addition to directly targeting risky injection practices. Ssafe trains and motivates PWID to better manage drug use to avoid situations and practices that promote risky injection (e.g., "binging" on drugs), and to implement health-protective behaviors (e.g., promoting risk-reduction norms in injection networks). Additionally, referral to existing LESHRC services will be encouraged including syringe exchange, overdose prevention, substance use treatment, and social services

5.8 Storage of samples for future analyses

All participants in part A will have plasma samples and/or dried blood spots (in event phlebotomy unavailable or unsuccessful) stored at the Weill Cornell Clinical and Translational Science Center laboratory. Future analyses will include HCV genotyping in instances of reinfection or treatment failure, and phylogenetic analyses of HCV virus. Participants in Part B will have samples stored when feasible, which we expect to be uncommon as laboratory testing will largely occur at community sites.

6. Clinical Management Issues

6.1 Chronic Kidney disease

Estimated GFR will be calculated based on the CKD-EPI formula based on baseline laboratory testing. Participants with chronic kidney disease stage 4 or 5, defined as estimated GFR < 30 mL/min, or those reporting hemodialysis will be discontinued from the study. Participants with any amount of chronic renal impairment will be counseled about the potential for a higher degree of side effects that may be observed in these groups, in accordance with national guidelines[39]

6.2 Cirrhosis and severe liver disease

Participants will have laboratory assessment for cirrhosis via FIB-4 as described in section 5.2. Participants with decompensated cirrhosis by physical exam, as determined by the treating physician on the basis of variceal bleeding, ascites, hepatic encephalopathy, or jaundice, will be discontinued from the study and referred to a hepatology specialist for co-management of cirrhosis and HCV. Participants compensated cirrhosis, after completion of HCV treatment, will be referred to primary care or hepatology for ongoing evaluation of cirrhosis including HCV screening.

6.3 Incident HIV infection

Participants who are initially HIV negative but seroconvert to HIV during the study will remain included in the study. They will be analyzed with the arm in which they were randomized. They will be offered to linkage to HIV primary care at an HIV provider local to them.

6.4 Pregnancy

Participants who initially have a negative pregnancy test but become pregnant during the study and are already on HCV treatment will be told the potential risks and benefits regarding continuation, and a joint decision between participant and provider will be made regarding continuation of therapy. Participants who are found to be pregnant before initiating therapy will not be started on treatment but remain in the study. Participants who become pregnant after treatment completion will remain in the study.

6.5 Hepatitis B Reactivation

Participants who have evidence of chronic HBV infection (positive HBV surface antigen) will be monitored for signs of reactivation including elevation of liver enzymes or clinical symptoms such as jaundice. Those who do have signs of reinfection will be provided with facilitated referral to an HBV treatment provider for treatment. Those who do not have evidence of HBV immunity (negative HBV surface antibody and negative HBV surface antigen) will be referred for HBV vaccination.

6.6 Treatment failure

Participants in the intervention arm with treatment failure, defined as positive HCV RNA PCR at end of treatment or post-treatment week 4, will be referred to a specialist office for further management of their HCV.

6.7 Hepatitis C Reinfection

Participants treated in the intervention arm who develop HCV reinfection as defined in section 5.5 will be referred to a specialist office for management of their HCV.

6.8 Incident hepatitis C infection

Participants with incident hepatitis C as defined in section 5.6 will be given options for treatment of their HCV. These may include enrollment in other studies (if eligible) or referral to an external provider for management of their HCV.

6.9 Drug Interactions

Participants will be assessed for the following drug interactions based on commonly observed co-administered medications: H2-receptor antagonists in doses exceeding famotidine 40mg twice daily, proton-pump inhibitors in doses exceeding omeprazole 20mg daily, amiodarone, digoxin, topotecan, phenytoin, phenobarbital, carbamazepine, oxcarbazepine, rifampin, rifapentine, rifabutin, St John's Wort, rosuvastatin at doses exceeding 10mg. Where alternatives can be found, they will be utilized in

conjunction with the prescribing provider. Participants with treatment-limiting drug interactions for which no alternative can be found will be excluded from study and referred to HCV treatment specialists off-site.

6.10 Storage and distribution of medications

Medications will be stored at the treatment site for immediate dispensation to enrollees as described above. These will be stored in a combination locked safe, for a maximum of 2 months, with temperature maintained below 30 deg C as detailed in the package insert.

7 Criteria for discontinuation

7.1 HCV treatment discontinuation

Participants in the intervention arm who discontinue HCV treatment prematurely for any reason will remain in the study. If more than 5 consecutive days of study medication were missed, the study investigator will advise treatment be held and offer HCV RNA testing. Based on these results, the study investigator will determine if re-initiation and completion of treatment should occur.

7.2 Study withdrawal and discontinuation

Participants may be withdrawn from the study at any time at their own request. They may also be discontinued from the study if, at any time, they are considered by study investigators to be unlikely to be able to participate in necessary follow up (e.g. due to severe illness, incarceration, change of residence). However, in keeping with the overall goal of the intervention, participants who are unwilling to partake in interviews or questionnaires, or undergo blood tests, will still remain in the study.

8 Statistical and analytic considerations

8.1 Sample size

Our own data (and others) suggests a SVR12 rate of 85% in active PWID (30), and existing literature suggests the control arm will have a very low uptake of HCV treatment (12% initiate treatment). (16) Using these estimates and an alpha =0.05, we have 100% power to detect a difference. However given the available referral and linkage programs, the control arm may have better HCV uptake and SVR 12 rates than predicted by literature. Assuming 41% (11/27) of participants in the control arm achieve SVR12, we will have 80% power to detect an SVR of 78% in the intervention arm.

In addition to have an adequate sample size to compare the primary end point of SVR12 rates with the control arm, a sample size of 27 HCV infected participants in Rapid Treatment arm allows for 90% power to show with reasonable certainty that the underlying true SVR12 rate is greater than 60% in the Rapid Treatment arm, assuming that this true rate is actually 85%.

The table below also shows two-sided exact Blyth-Still-Casella (BSC) 90% CIs for potential observed SVR proportions for 27 enrolled participants. With a HCV infected sample size of 27 participants, the CI for the true SVR12 rate will be entirely above 60% if 21 or more of the 27 participants achieve SVR12.

Patients enrolled and found not to have detectable HCV RNA will be replaced. Assuming 75% of HCV antibody positive individuals will be infected with HCV (positive HCV RNA), we anticipate have to enroll roughly 36 participants in each arm to acquire 27 with confirmed viremia.

Observed SVR12 Rate	90% CI for True SVR12 Rate
85% (23/27)	(71%, 93%)
81% (22/27)	(65%, 90%)
78% (21/27)	(62%, 90%)
74% (20/27)	(58%, 85%)
70% (19/27)	(54%, 84%)
67% (18/27)	(50%, 80%)

As of this amendment, data from part A will be analyzed based on enrollment through March 1 2020, so the power to detect a difference will be reduced from the above calculation. This is due to the break in enrollment that was necessary during the COVID-19 pandemic.

8.2 Randomization

Participants will be randomly assigned to the intervention or control condition in a 1:1 ratio using randomly permuted blocks. Participants randomized in the intervention arm will receive medical evaluation and distribution of "starter pack." Participants in the control arm will be provided referral to community HCV providers.

8.3 Data Analysis

8.3.1 Analysis of clinical outcomes data

For the primary analysis, after the completion of part A, we will compare the proportion of patients who achieve SVR12 in each arm using Chi-square or Fishers' exact testing, using an intention-to-treat approach in which participants are analyzed in the group to which they are randomized. Participants with negative confirmatory HCV RNA PCR tests on study entry will not be included in the analysis.

For secondary analyses, we will:

- Compare the proportion of patients who achieve end-of-treatment response using Chi-square or Fishers' exact testing
- Compare the proportion of patients who complete treatment, using Chi-square or Fishers' exact testing
- Compare the proportion of patients who have HCV reinfection, using Chi-square or Fishers' exact testing
- Describe adherence for participants in the Intervention arm only
- Describe demographic, clinical and behavioral factors for participants who have HCV reinfection or incident HCV infection

We will also perform the same analyses using an "as-treated" approach, in which participants in the intervention arm will not be included if they failed to initiate HCV treatment, or discontinued treatment for reasons clearly unrelated to the treatment intervention (e.g. relocation, incarceration).

After the completion of part B, we will compare the proportion of patients who achieve SVR12 in each Part B telemedicine to (1)Part A intervention (2) Part A control, using Chi-square or Fishers' exact testing, using an intention-to-treat approach in which participants are analyzed in the group to which they are randomized. Participants with negative confirmatory HCV RNA PCR tests on study entry will not be included in the analysis.

8.3.2 Analyses for qualitative data

A subset of patients will be selected for qualitative interview from each arm. Participants will be recruited using purposive sampling, aiming for diversity of demographic characteristics, HCV risk factors, and treatment outcomes. Qualitative interviews will be analyzed using content analysis, creating codes and synthesizing them into dominant themes.

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