A precision randomized trial to evaluate the impact of tailored hepatitis C virus (HCV) treatment adherence support on HCV treatment outcomes in HIV/HCV co-infected and HCV mono-infected people who inject drugs (PWID) in India

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Supporting Treatment Outcomes among PWID (The STOP-C Study)

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2. SIGNATURE PAGE

I agree to conduct the study in accordance with the relevant, current protocol and will not make changes to the protocol without permission of DAIDS, except when necessary to protect the safety, rights, or welfare of study participants.

I agree to personally conduct or supervise this study.

I will ensure that the requirements relating to obtaining informed consent and Ethics Committee (EC) or Institutional Review Board (IRB) review and approval (insert relevant terms of assurance here, e.g. 45 CFR 46, ICH/GCP, etc.) are met.

I agree to report to the sponsor adverse experiences as per that occur during the course of this study.

I agree to maintain adequate and accurate study records and to make those records available for inspection by DAIDS, DAIDS' authorized representatives, and/or other applicable regulatory entities.

I will ensure that an EC or IRB that complies with the requirements of 45 CFR Part 46 will complete initial and continuing review and approval of the study. I also agree to promptly report to the EC/IRB all changes to the study and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes to the study without DAIDS and EC/IRB approval, except where necessary to eliminate apparent immediate hazards to study participants.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

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5. LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ART	Antiretroviral Therapy
AST	Aspartate Aminotransferase
ATV	Atazanavir
CD4	Cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
CTP	Childs Turcotte Pugh
CrCl	Calculated creatinine clearance
Ag	Antigen
DAA	Direct Acting Antivirals
DAIDS	Division of AIDS
DOT	Directly Observed Therapy
DPRS	DAIDS Protocol Registration System
DSM	Data, Safety and Monitoring
DSMB	Data and Safety Monitoring Board
DTG	Dolutegravir
EAE	Expedited Adverse Events
eCRF	electronic Case Reports Forms
EFV	Efavirenz
EHR	Electronic Health Record
ERP	Expert Review Panel
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
FGD	Focus Group Discussion
FIB-4	Fibrosis-4 score
FSH	Follicle Stimulating Hormone-release factor
FTC	Emtricitabine
GGT	Gamma-glutamyl transferase
GCP	Good Clinical Practices
GCLP	Good Clinical Laboratory Practices
Hb	Hemoglobin
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCT	HIV Counseling and Testing
HIV	Human Immunodeficiency Virus
ICC	Integrated Care Center
INASL	Indian National Association for the Study of Liver Disease
INR	Internalized Normal Ratio
IRB	Institutional Review Board
IU	International Units
IUD	Intrauterine Device
JHMI	Johns Hopkins Medical Institution
JHU	Johns Hopkins University
LLOQ	Lower Limit of Quantification
LMIC	Low-and-Middle-Income Countries

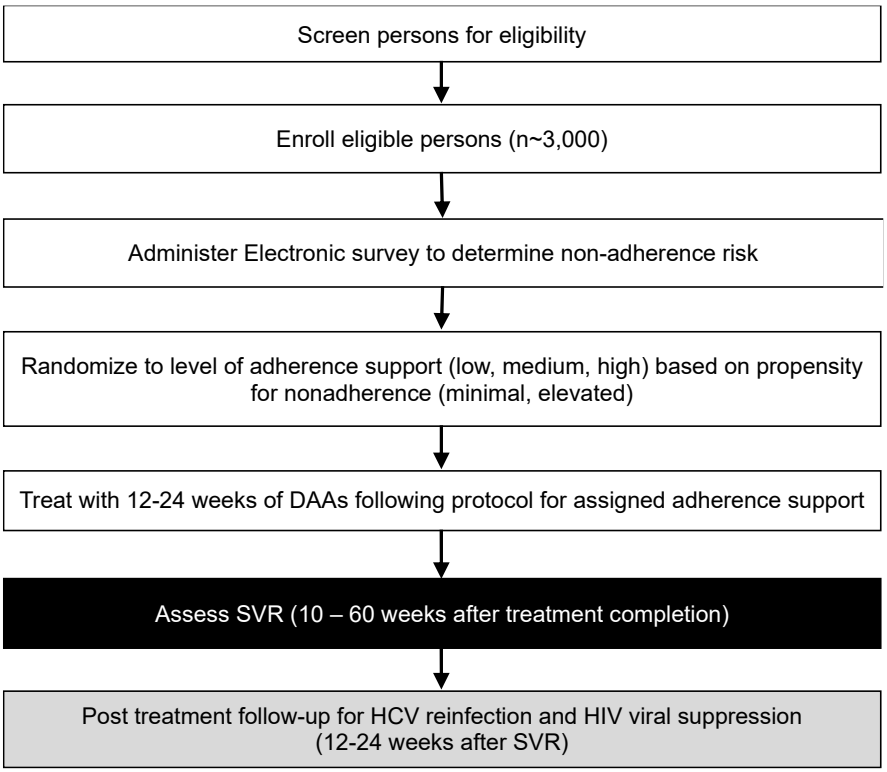
MSM	Men who have Sex with Men
MTB	Mycobacterium Tuberculosis
MOP	Manual of Operations
NGO	Non-governmental Organization
NIAID	National Institute of Allergy and Infectious Disease
NS5A	Nonstructural Protein 5A
NS5B	Nonstructural Protein 5B
OAT	Opioid Agonist Therapy
OHRP	Office for Human Research Protections
PI	Principal Investigator
PN	Patient Navigation/Patient Navigator
PWID	People Who Infect Drugs
POC	Point Of Care
RAS	Resistance-Associated Substitutions
RBC	Red Blood Cell
RBV	Ribavirin
RCT	Randomized Control Trial
RDS	Respondent-Driven Sampling
RNTCP	Revised National Tuberculosis Program
RR	Relative Risk
RSC	Regulatory Support Center (DAIDS)
SAE	Serious Adverse Event
SOF	Sofosbuvir
SOF/DAC	Sofosbuvir/Daclatasvir
SOF/VEL	Sofosbuvir/Velpatasvir
SSP	Syringe Services Program
STI	Sexually Transmitted Infection
SVR	Sustained Virologic Response
TDF	Tenofovir
TB	Tuberculosis
ULN	Upper Limit of the Normal range
WBC	White Blood Cells
WHO	World Health Organization
YRGCARE	Y.R. Gaitonde Centre for AIDS Research and Education

6. PROTOCOL SUMMARY

Full Title:	A precision randomized trial to evaluate the impact of tailored hepatitis C virus (HCV) treatment adherence support on HCV treatment outcomes in HIV/HCV co-infected and HCV mono-infected people who inject drugs (PWID) in India
Short Title:	Supporting Treatment Outcomes among PWID (The STOP-C Study)
Sample Size:	3000
Study Population:	HCV-infected, treatment-naïve PWID receiving care in integrated HIV/HCV prevention and treatment centers (ICCs) in 7 cities across India
Participating Sites:	1. YRGCARE ICC at SHALOM in Aizawl, Mizoram 2. YRGCARE ICC at Gurunanak Dev Medical College, Amritsar, Punjab 3. YRCARE ICC at Government District Hospital, Bilaspur, Chhattisgarh 4. YRGCARE ICC at SHALOM in Churachandpur, Manipur 5. YRGCARE ICC at GSVM Government Medical College, Kanpur, Uttar Pradesh 6. YRGCARE ICC at Civil Hospital, Ludhiana, Punjab 7. YRGCARE ICC at Kotwalli Police Station, New Delhi
Study Design:	Individual-level randomized clinical trial with unbalanced allocation according to estimated propensity for non-adherence at baseline
Study Duration:	3 years including 12-24 weeks on study intervention (adherence support) and up to 4 years of post-treatment follow-up
Study Regimen/ Intervention	Three intensity levels of treatment adherence support will be compared in participants treated with direct acting antiviral (DAA) regimens for HCV. 1) Low intensity support: 4-weekly dispensation with standard adherence counseling and tracking for missed medication refill visits 2) Moderate intensity support: 4-weekly dispensation with tailored patient navigation support for medication reminders, attending medication refill visits, overcoming barriers and service linkage 3) High intensity support: patient-centered directly observed therapy with patient navigation support for overcoming barriers and service linkage
Primary Objective:	To evaluate whether the intensity of treatment adherence support affects sustained virologic response rates in HCV mono- and HIV/HCV co-infected participants receiving HCV DAAs in PWID-focused centers

Primary Endpoint: Sustained virologic response (SVR) defined as HCV RNA less than the lower limit of quantification (LLOQ) 10 – 60 weeks after treatment completion

Study Schema:



Schedule of Procedures/ Evaluations: See **Section 12.1**

7. INTRODUCTION

7.1 Background Information

7.1.1. Towards elimination of hepatitis C virus infection

In 2015, ~71 million persons were chronically infected with HCV, of whom 90% were in low-and-middle-income countries (LMICs)[1] and ~5% were coinfected with HIV.[2] Chronic HCV progresses more rapidly in those co-infected with HIV[3-10] and as HIV mortality has declined, HCV mortality has increased and eclipsed HIV mortality in some settings.[11,12] HCV can now be cured with 8 to 12 weeks of all oral, safe, highly efficacious direct acting antivirals (DAA).[13-18] The single tablet regimen of sofosbuvir/velpatasvir (SOF/VEL) achieves cure in greater than 95% of those who receive treatment, and cure rates are comparable across all genotypes.[14-16] With these developments, the World Health Organization (WHO) released HCV elimination targets for 2030[19] calling for an 80% reduction in HCV incidence and 65% reduction in mortality. To achieve these goals, 90% of HCV infected individuals must be diagnosed and 80% of those diagnosed must be treated, requiring massive scale-up in countries where to date less than 5% have been treated. These targets will be facilitated by licensing, preferential pricing, and production of generic DAAs that have reduced cost to ~US $ 150/course in settings like India.[20]

7.1.2. HCV elimination efforts need to focus on PWID by leveraging HIV efforts

People who inject drugs (PWID) are disproportionately affected by HCV, bearing a burden 10 to 100 times that of the general population, with HIV-infected PWID almost always being HCV coinfected.[2,21] To truly interrupt HCV transmission and achieve elimination whether on a macro- or micro- scale, WHO targets need to be met in all populations including PWID. However, experience with HIV suggests that in the absence of targeted efforts, national programs generally fail to reach PWID in countries with key population focused HIV epidemics. However, there is an opportunity to leverage infrastructure built for HIV to deliver HCV care. Indeed, three recent meta-analyses identified that co-location of HCV testing, treatment and other services significantly improved HCV treatment outcomes.[22-24] However, these reviews also noted that despite the potential synergies, positive health impact and potential cost savings, there is limited knowledge on the optimal integrated service delivery model, particularly in LMICs.[22-24]

7.1.3. Preliminary work: An integrated service delivery model for HIV prevention and treatment in India

In 2012, we initiated a 22-city cluster-randomized trial to evaluate the effectiveness of integrated care centers (ICCs) to improve HIV outcomes in key populations (strata for PWID and men who have sex with men [MSM]) across India (DA032059; MH89266; ClinicalTrials.gov identifier: NCT01686750).[25] The trial was designed to determine the community impact of ICCs measured by serial cross-sectional surveys prior to and two years after the implementation of the ICC intervention. Samples were accrued using respondent-driven sampling (RDS), which is designed to produce unbiased prevalence estimates in hidden populations.[26,27]

Between September 2012 and October 2013, we completed pre-intervention RDS surveys in 27 cities (~1000 per city). Using these data, we randomized 22 sites to intervention or control at a 1:1

allocation ratio using stratified, restricted randomization. PWID and MSM-focused ICCs were initiated in 11 intervention sites in June 2014. Venues (non-governmental organizations [NGOs] or government facilities) were selected for scale-up following discussions between the Indian government, NGO leaders, community members, and investigators. In the PWID stratum of this trial, ICCs were scaled from existing opioid agonist treatment (OAT) centers to incorporate other risk reduction services including syringe services programs (SSP) and HIV counseling and testing (HCT). Some medical services at these ICCs are provided on-site including sexually transmitted infection (STI) treatment while others are provided through peer navigated referral (e.g., tuberculosis treatment, antiretroviral therapy [ART]).

After 2 years, a second (post-intervention) RDS was conducted in all 22 sites from October 2016 and May 2017. ICCs resulted in significant improvements in HIV testing, but limited ART uptake.[28] In response, we launched a second phase to evaluate supplementing ICCs with demand-side incentives for HIV care (DA041034; ClinicalTrials.gov identifier: NCT02969915). Of the prior sites, 16 were selected based on HIV prevalence and poor care engagement (8 PWID, 8 MSM). ICCs have been scaled in all cities with half randomized to receive incentives for HIV care. A third cross-sectional sample will be accrued in late 2020 to evaluate community impact of the incentives. This protocol will take place in 7 of the 8 PWID ICCs in this ongoing trial (**Figure 7.1.1**). One of the 8 sites is being excluded due to low HCV prevalence.

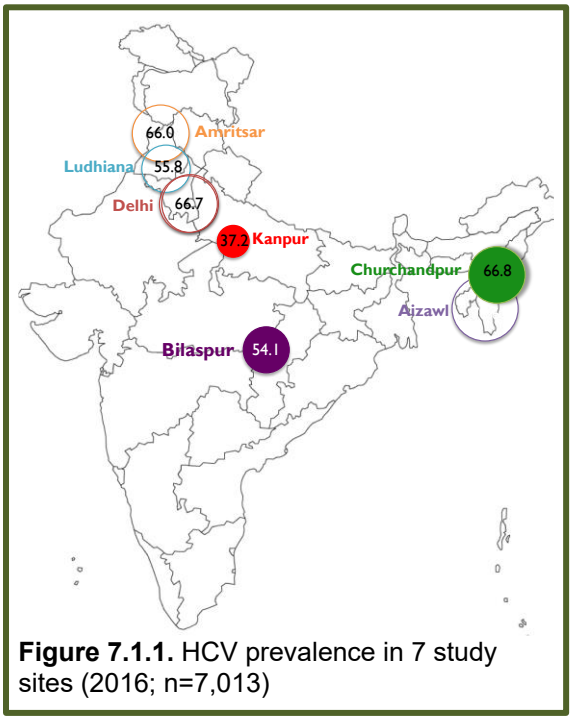


Figure 7.1.1. HCV prevalence in 7 study sites (2016; n=7,013)

7.1.4. High burden of HCV among PWID in India but poor engagement across the HCV care continuum

In the 2013 baseline assessment for the aforementioned trial, 14,481 PWID were recruited in 15 cities (~1000 per city) across India.[29] HCV prevalence ranged from 4.9 – 64.9% in the 15 cities.[30] Only 1,272 (7%) had ever been tested for HCV and the most common reason for not having been tested was never having heard of HCV (51%) followed by low risk perception. Of 5,777 PWID with evidence of HCV infection, only 5.6% were aware of their HCV positive status. In 2016, at the evaluation survey, HCV prevalence ranged from 37.2 to 76.6% in the 7 proposed sites (**Figure 7.1**).

7.1.5. Impact of integrating HCV testing into ICCs

In 2015, we received separate funding to integrate HCV testing into the 6 PWID-focused ICCs. Over 12 months, 6,486 clients across the five of six PWID focused ICCs that implemented HCV testing during the intervention period had an HCV antibody test, of whom 3,046 (47%) tested positive. We evaluated community-level impact by comparing outcomes in the evaluation RDS survey in 6 sites with ICCs and 6 without. Adjusting for baseline levels of HCV testing, the prevalence of ever having had an HCV test was 3.8 times higher in ICC vs. control sites (95% CI: 1.4, 10.3). Similarly, awareness of HCV status among those positive was 7.11 times higher in ICC vs. control sites (95% CI: 1.4, 44.3; **Figure 7.1.2**). There was only marginal non-significant

improvement in linkage to care and treatment uptake. During this period, no-onsite HCV care was provided; ICC clients who tested positive were referred to government centers for HCV care and treatment.

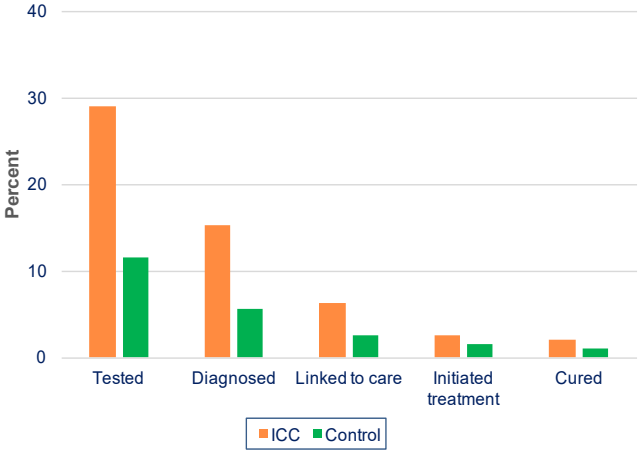


Figure 7.1.2 HCV care continuum after HCV testing integration in ICC vs. control cities

7.1.6. Some PWID may need additional support to optimize HCV treatment outcomes

As programs shift towards HCV treatment delivery, they need to consider factors other than provision of free medications. Even with short treatment duration, there are concerns about adherence and reinfection particularly in persons with substance use disorder.[30-37] Limited data from clinical trials and observational studies in the DAA era suggest that high adherence among PWID is possible with optimal support (e.g., OAT, group counseling, directly-observed therapy [DOT]) but these derive from highly selected patients.[17,38-41] It is unclear whether community-based PWID, particularly those in LMICs, can achieve the same levels of adherence without additional support.

Moreover, reinfection data are also sparse. [42-45] Data that do exist suggest variable reinfection rates across different groups. In addition, dynamic modeling supports that integration of HCV treatment with harm reduction can reduce HCV reinfection risk.[46,47] However, there are structural barriers (e.g., infrastructure, human capital) that will impact how programs can provide intensive support to all those treated.[31,34] Identifying who can be cured with minimal intervention and who will need more support can improve efficiencies. We will evaluate a novel “precision” approach to allocating treatment support based on need allowing us to estimate efficacy within strata of risk for treatment failure (minimal/elevated risk) while still allowing estimation of the average treatment effect.

7.1.7. Prior experience with support strategies

Our team followed a cohort of PWID in Chennai, India for >10 years[48,49] with high HCV prevalence[21,48] and high HIV and HCV-related mortality.[9,50] In a survey administered to 541 participants in this cohort in 2016,[51] we found that willingness to undergo HCV treatment differed by HIV status. Moreover, we found that willingness to undergo treatment increased with perceptions related to decreasing treatment duration, higher perceived efficacy, fewer side effects, pills vs. interferon and reduced cost. Interestingly, 70% reported that they were more willing to undergo HCV treatment if they had to come in every day to the clinic to get a treatment dose rather than going home with a month’s supply (P=0.001). This may reflect general acceptability of DOT, the cornerstone of tuberculosis (TB) therapy in India, but regardless provides motivation for incorporating DOT-based strategies as an adherence support strategy in this study.

7.1.8. Delivering HCV treatment to PWID in India using a field-based directly observed therapy strategy

As passive referral for HCV treatment did not improve outcomes in our Chennai cohort, in September 2015, we launched a randomized trial to evaluate the feasibility of field-based DOT (n=50) comparing two arms: 12 weeks of SOF+pegylated interferon+ribavirin (RBV) to 24 weeks of SOF+RBV.[40] These were the only two pan-genotypic regimens available in India at the time. Clinicians providing HCV treatment in this study were trained by the Johns Hopkins Viral Hepatitis Center's Sharing the Cure program. Treatment was delivered from a 1000 square foot site, staffed by two part-time clinicians, two nurses, a site manager, a phlebotomist and 3 outreach workers all of whom were also providing clinical services to PWID outside the trial.[48,49] Three field workers delivered medication daily to participants at a location of their choosing; dosing was confirmed using a biometric device.

In this trial, treatment completion was achieved by 88% in each arm. While ongoing drug injection was only reported by a minority in this sample, greater than 50% reported active use of some substance. For persons on the 12-week regimen, the median number of doses missed per person was 4. In addition, 40% of participants requested take-home doses at some point during the 12 weeks (median: 2.5 doses per person requesting). The primary reason for requesting take home doses was travel. Importantly in the arm that received 12-weeks of therapy, there was no difference in treatment completion or SVR by ongoing drug use.

These data speak to the feasibility of field-based DOT and its success in persons with ongoing substance use. In this study, one field worker was able to manage about 30 clients at a time. However, there were some logistical challenges, and it was clear that some clients could have maintained high adherence without daily contact. This provides the rationale for our current protocol where this strategy will not be used for all participants randomized to the high intensity support strategy but will be assigned to clients with very specific support needs/barriers.

7.1.9. Description of study field sites

As part of the trial described above in **Section 7.1.3**, PWID focused ICCs have been scaled by the Johns Hopkins University (JHU)-YRGCARE team across 7 Indian cities. Three ICCs (Aizawl, Mizoram; Bilaspur, Chhattisgarh; Ludhiana, Punjab) were opened in 2015 and four (Amritsar, Punjab; Churachandpur, Manipur; Kanpur, Uttar Pradesh; New Delhi) were opened in 2017. Details on the locations, existing staff and client base of these ICCs can be found in **Table 7.1.** All except for Kanpur were scaled from existing OAT programs. In India, OAT is provided free-of-charge by the government of India. In some cities, OAT is dispensed within government centers and in others it is dispensed through NGOs. In one city, Delhi, a new facility was established adjacent to the government OAT program.

These are truly community-based low threshold care centers. Each of the ICCs is equipped with separate rooms/designated areas for 1) the coordinator of site activities; 2) provision of OAT; 3) patient examination; 4) laboratory specimen collection and processing; 5) counseling; and 6) research activities/interviewing. Each laboratory has been certified by the YRGCARE Infectious Disease Laboratory prior to the beginning of any research activities. Each site has space for a study pharmacy.

Each site is already staffed with a 1) Site Coordinator; 2) Research Coordinator; 3) Counselor; 4) 1-2 Nurses (one for the dispensation of OAT and one for management of STIs, TB, skin and soft

tissue infections and other health conditions); 5) Laboratory technician/phlebotomist; and 6) 1-3 outreach workers commensurate with client volume.

Table 7.1. Integrated HIV/harm reduction centers (ICCs) across India

City	Location	Government/ NGO	Current staff	Clients registered
Northeastern India				
Aizawl, Mizoram	SHALOM Lower Zarkawat	NGO	7	2,055
Churachandpur, Manipur	SHALOM	NGO	7	837
Northern India				
Amritsar, Punjab	Gurunanak Dev Medical College, OST Center Mathija Road	Government	8	1,573
Ludhiana Punjab	Civil Hospital Field Ganj Road CMC Campus	Government	8	3,430
New Delhi	Kotwalli Police Station Chandni Chowk	Adjacent to government OST	7	910
Central India				
Bilaspur, Chhattisgarh	Government District Hospital	Government	7	1,569
Kanpur, Uttar Pradesh	GSVM, Government Medical College, Swarup Nagar	Government	7	919

7.2 Rationale

In order to achieve WHO targets, programs must improve the entire HCV care continuum from diagnosis to cure to prevention of reinfection. PWID face barriers at each step (**Figure 7.2**). The goal of this protocol is to improve HCV care continuum outcomes for PWID, reduce potential onward transmission to others and improve HIV outcomes among those who are HIV/HCV coinfected.

7.2.1. Rationale for delivering HCV treatment through community-based settings

There is an evidence base from other LMICs including Vietnam and the Ukraine that community-based OAT and SSP programs may provide a basis for delivering medical services.[52-54] Our group has demonstrated that integrating HCV testing with HIV and harm reduction services can improve early HCV care continuum steps. However, without on-site treatment, there was limited improvement in downstream HCV

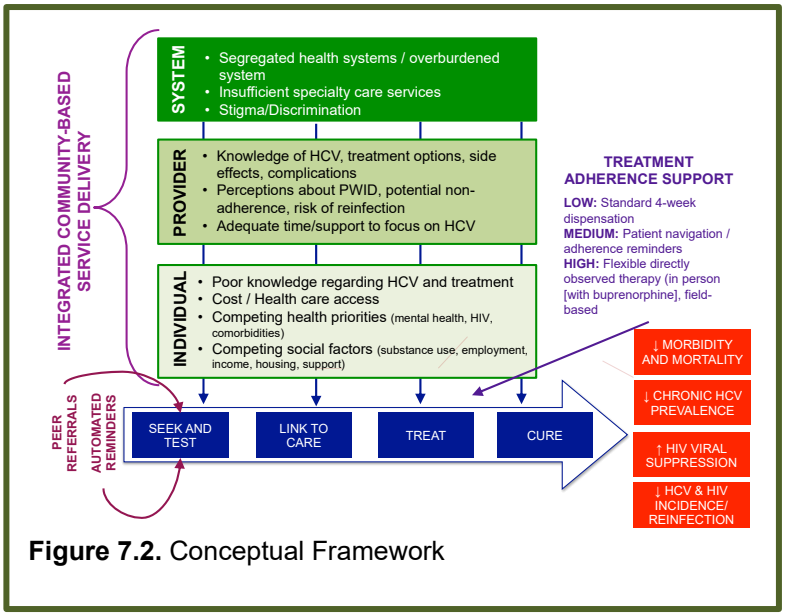


Figure 7.2. Conceptual Framework

care continuum steps. There is also increasing support for decentralizing HIV care and treatment through community-based clinics and community health workers. The simplification of HCV treatment lends itself to such a model where the majority of care and treatment is provided by nurses, pharmacists and peer health workers, thereby reducing costs associated with the provision of treatment. Moreover, for disenfranchised populations like PWID, provision of care in community-based settings can reduce stigma and discrimination. The goal is that the structural component of this intervention will improve the first three steps of the HCV care continuum, specifically seek and test, link to care and treat.

7.2.2. Rationale for provision of treatment adherence support and the support strategies

Since DAAs only became widely available after 2014, there is a dearth of literature on interventions to support treatment adherence in the DAA era. The majority of data on HCV treatment outcomes among PWID in the DAA era derive from controlled trials with select groups of patients with some limited additional data from observational studies. Yet, even these observational studies include highly select groups of patients many of whom are former rather than current PWID. So, while these data collectively suggest that high adherence among PWID is possible with optimal support (e.g., OAT, group counseling, directly-observed therapy [DOT]),[17,38-41] it is unclear whether community-based PWID, particularly those in LMICs can achieve the same levels of adherence without additional support.[30-37]

Nearly all of the data on evidence-based interventions to support engagement in and completion of treatment derive from the interferon era. In a recently completed systematic review of evidence-based interventions from PubMed, Medline, Google Scholar, EmBASE, and PsychInfo bibliographic databases and citation indices,[24] interventions to enhance HCV assessment, treatment, and adherence were identified in 4 categories: 1) diagnosis; 2) linkage to care (n=29); 3) pre-therapeutic evaluation or treatment initiation (n=15); or 4) treatment adherence (n=33). Several of these interventions introduced on-site HCV care for patients in previously established OAT programs and showed comparable rates of uptake and SVR as in non-PWID populations.[55-60] A key component of all of these interventions was a multidisciplinary approach that combined medical and addiction treatment with intensive social support.[61] Additional studies demonstrated that patients with ongoing drug use and psychiatric comorbidity could be effectively linked to care and treated within primary care settings.[58,62-66] Evidence has also supported high treatment uptake and SVR with peer-driven interventions including weekly support groups.[67-69]

Several lines of evidence from the pre-DAA era support the interventions proposed in this trial. In studies where PWID have been surveyed about HCV treatment knowledge, barriers to treatment initiation,[70] and interest, and willingness in receiving treatment,[71] treatment-naïve patients have been more willing to receive HCV treatment when they perceived themselves at risk for cirrhosis or liver cancer[72] or had more knowledge about HCV.[71] Moreover, a randomized control trial (RCT) of a patient navigation intervention consisting of motivational interviewing, education, and case management was associated with increased HCV clinic visit attendance among patients in methadone maintenance.[73]

In the pre-DAA era, several interventions evaluated the impact of provision of HCV treatment through DOT. By using a modified DOT approach (mDOT) to observe only the morning dose of ribavirin or weekly injections of interferon, HCV treatment was successfully delivered in OAT programs,[57,58,74] prison settings,[75] and community health centers.[67] Another study provided

ribavirin as once-daily DOT, demonstrating extremely high rates of SVR among patients stably maintained on OAT.[76]

While these data collectively provide support for multidisciplinary care and the interventions that will be used in this trial, the optimal model for supporting high HCV treatment adherence in the DAA era remains unknown. First, it is unclear that the intensive support required during interferon-based therapy will be needed with DAAs given the difference in treatment duration and side effect profile. It has been argued that additional supportive interventions like PN and DOT may not be required in the context of treatment simplification and that indeed this additional support may be overly burdensome. On the other hand, the majority of data available in the DAA era derive from clinical trial patients and cannot be generalized to community-based patients.

The current standard of care in India and in most LMICs is dispensation of a 4-week supply of medication along with minimal counseling. There is nearly no data from LMIC settings.

7.2.3. Rationale for the unbalanced allocation approach (precision trial)

Prior trials evaluating the impact of HCV adherence support interventions among PWID have used standard approaches that randomize groups of individuals to different interventions or to a single intervention vs. the standard of care. This approach assumes that all of those assigned to an intervention have the same need for the intervention and the potential to benefit equally from the intervention. However, while the data do support that at least some PWID will need additional support to achieve cure, there are structural barriers (e.g., infrastructure, human capital) that limit the capacity to provide intensive support to all those treated, particularly in settings with high burden.[31,34] Identifying who can be cured with minimal intervention and who will need more support can potentially improve efficiencies.

This protocol utilizes a “precision” approach to allocating treatment support based on need allowing us to estimate efficacy within strata of risk for treatment failure (minimal/elevated risk) while still allowing estimation of the average treatment effect. This approach is similar to stratified randomization with the modification that treatment allocation is not equal across strata. This targeted randomization actually induces confounding (because the prognostic score is based on factors that influence the outcome) that needs to be accounted for in the analysis (**see Section 15**). However, because of randomization, the factors used in determining propensity for failure will be balanced in expectation, as this is analogous to a propensity score, which balances included covariates. Thus, using a single approach, we can answer multiple questions related to both the efficacy of the support strategy for persons at different levels of risk for failure as well as the impact in the total population of a particular support strategy.

7.2.4. Potential impact of trial

Both of the behavioral interventions in this trial rely on the support of nurses and peer/community health workers. In many LMIC settings, high healthcare costs, infrastructure gaps and general shortages in physicians and nurses have led to increased use of community health workers to deliver care for HIV, tuberculosis and increasingly non-communicable diseases.[77-79] Indeed, the WHO has supported such a strategy for HIV in response to issues around shortages. In general community health workers are members of communities where they work and are supported by the health system but tend to have less structured training than nurses and others in the formal health care system. The idea is that these health workers provide a bridge between the health care system and the community, deliver low cost primary health care services and can facilitate

engagement in and continuity in care. These programs range in scope from large national programs to smaller community focused initiatives that have demonstrated increased coverage of health services particularly in remote areas and improved outcomes related to HIV and some non-communicable diseases.[80-83] In these settings, the cost associated with these workers is relatively modest.

In India specifically, the National AIDS Control program has recognized the need for decentralizing services as well as the importance of navigators, who are analogous to community health workers, for improving HIV outcomes from testing to linkage to HIV viral suppression.[84] The National Program is already supporting a cadre of such staff in government-based testing and treatment centers and non-governmental organizations. Through partnership between USAID, the National AIDS Control Organization and investigators on this study team, India is also exploring home-based HIV testing and treatment. Moreover, India has a culture of DOT with TB treatment and current requirements for buprenorphine for OAT including daily pickups (including on Sundays).[85-87]

Thus, there is a precedent for the types of low-cost support interventions being evaluated in this trial. Moreover, formal cost analyses are planned as part of the parent grant and so will further inform adoption of these interventions by the Indian government and other LMIC settings.

7.3 Study Hypotheses

1. Among PWID at elevated risk for treatment failure, PWID receiving the high intensity intervention will have significantly higher SVR than those receiving either the medium or low intensity interventions.

   1a. Among PWID at minimal risk of treatment failure, PWID receiving either the high or medium intensity intervention will have significantly higher SVR than those receiving the low intensity intervention.

2. Among PWID at elevated risk for treatment failure, PWID receiving the high intensity intervention will have significantly higher treatment completion than those receiving either the medium or low intensity interventions.

   2a. Among PWID at minimal risk of treatment failure, PWID receiving either the high or medium intensity intervention will have significantly higher treatment completion than those receiving the low intensity intervention.

3. Among PWID at elevated risk for treatment failure, PWID receiving the high intensity intervention will have significantly higher adherence than those receiving either the medium or low intensity interventions.

   3a. Among PWID at minimal risk of treatment failure, PWID receiving either the high or medium intensity intervention will have significantly higher adherence than those receiving the low intensity intervention.

4. HCV reinfection rates will be lower among clients who have high engagement with OAT.

5. Among HIV/HCV co-infected PWID, HIV viral suppression will be higher after achievement of HCV cure.

8. OBJECTIVES

The overall goal of this protocol is to evaluate whether HCV treatment outcomes (sustained virologic response, treatment completion, adherence) and post treatment outcomes (HCV reinfection, HIV viral suppression) in HCV mono- and HIV/HCV co-infected PWID can be optimized by tailoring treatment support in 7 PWID-focused integrated HIV/HCV prevention treatment centers.

8.1 Primary Objective(s)

To evaluate whether the intensity of treatment adherence support affects sustained virologic response rates in HCV mono- and HIV/HCV co-infected participants receiving HCV DAAs in PWID-focused centers.

8.2 Secondary Objective(s)

1. To evaluate whether the intensity of treatment adherence support affects HCV treatment completion rates.

2. To evaluate whether the intensity of treatment adherence support affects HCV treatment adherence.

3. To estimate the incidence and correlates of HCV reinfection among HCV mono- and HIV/HCV coinfected PWID who achieve HCV cure.

4. To evaluate the impact of HCV cure on HIV viral suppression among HIV/HCV coinfected PWID.

9. STUDY DESIGN

This is a 3-arm, individual-level randomized clinical trial, in which treatment assignment probabilities vary according to participants' estimated propensity for treatment failure at baseline (precision randomization). Minimal risk individuals have a higher likelihood of being allocated to lower intensity intervention and elevated risk individuals have higher likelihood of being allocated to higher intensity intervention. An estimated 3,000 persons will be enrolled and randomized at 7 integrated care centers (ICCs) across India across a duration of 18 – 24 months. All persons who are receiving care in one of the 7 YRGCARE ICCs, who are eligible for HCV treatment according to standard criteria and provide written informed consent will be screened for eligibility. Using a 'precision clinical trial' approach, HCV treatment adherence support will be assigned using an unbalanced allocation method weighted by an individual's propensity for treatment failure.

Data from these 7 ICCs on early ART refills/HIV viral suppression (3-6 months after ART initiation) will be used to develop and validate an algorithm to predict propensity for HCV treatment failure. The optimal cutoff for the algorithm will be based on the combination of data used to develop the algorithm and data from community-based samples in each of these sites. Prior to treatment initiation, each participant will undergo a questionnaire to capture information on barriers/ facilitators to treatment adherence identified in the prediction model in order to determine the propensity for HCV treatment failure (minimal or elevated risk). Based on preliminary analysis, groups will be defined by the median of the score (below the median: minimal risk; above the median: elevated risk), but this may be modified depending on performance of the final algorithm. Individuals will be preferentially randomized to the support level that matches their failure risk. Those at elevated risk for treatment failure will be randomized at an allocation ratio of 3:2:1 for Arm 3 (high intensity support), Arm 2 (medium intensity support) and Arm 1 (low intensity support), respectively. Conversely, those at minimal risk will be randomized at a ratio of 1:2:3 to Arm 3 (high intensity support), Arm 2 (medium intensity support) and Arm 1 (low intensity support), respectively. Participants and study staff will be blinded to the risk classification (minimal, elevated) but, because of the nature of the interventions, blinding to intervention assignment is not possible.

Arm 1: Low intensity intervention: We will dispense 28-day supplies of medication at baseline, 4 weeks, and 8 weeks. Participants will receive standard adherence counseling at entry and every refill pickup/home or field delivery. Participants will have access to all of the services available at the ICC including facilitated linkage to referrals as needed. Patient Navigators will routinely track clients who miss refill appointments in real-time using standard tracking measurements.

Arm 2: Medium intensity intervention: The medium intensity intervention will include standard of care dispensation of 28-day supplies of medication at baseline, 4 weeks and 8 weeks. Participants will be assigned to a PN and receive tailored patient navigation support for medication reminders, picking up medication refills (or home or field delivery of study medications), overcoming barriers as well as service linkage.

Arm 3: High intensity intervention: The high intensity intervention will involve patient-centered DOT with flexibility in terms of the frequency of pickup and the site of DOT (ICC, field-based) with a minimum of at least 1 observed dose per week. Participants in this arm will also receive PN support for overcoming barriers and service linkage similar to participants in Arm 2. The main differences between Arms 2 and 3 are: (i) medications will not be dispensed for more than one week at a time (to coincide with OAT dosing, where applicable); and (ii) ≥1 dose/week will be observed.

To measure adherence, brief surveys and pill counts will be conducted at each medication pick up/ drop off. In the high intensity intervention, a computerized system will track client doses that are observed using biometrics, including doses delivered in the field.

Persons will be treated for HCV according to the standard of care in India. Minimal laboratory monitoring will be used except when clinically indicated. Clients with decompensated cirrhosis will be excluded from treatment.

All HIV/HCV co-infected participants and those HCV mono-infected participants who achieve SVR will be followed post SVR assessment. These individuals will be followed every six months after the SVR assessment to assess HCV reinfection and HIV viral suppression (among HIV/HCV coinfected participants) for up to 48 months after SVR. In each ICC, an electronic health record (EHR) is already in place. This system captures information on general patient characteristics,

medical history including diagnoses, laboratory testing, and treatment received including systematic assessment of ART refills. The system is designed to capture information on care delivered in the ICC (e.g., OAT, SSP) and other government centers (e.g., TB treatment). All treatment dispensation, adherence, and treatment outcomes including HCV RNA testing will be captured in this database. Re-infection will be assessed using the Abbott ARCHITECT HCV Ag assay which is highly sensitive (97-100%) in identifying HCV RNA[88,89] and in a small study of re-infection demonstrated 100% sensitivity/specificity of identifying recurrence of virus post-SVR.[90]

10. STUDY POPULATION

The target population is PWID who are actively infected with HCV in each of the 7 study cities. Currently, there are 11,293 PWID who have registered for services at one off the 7 ICCs. **Table 10.1** describes the characteristics of current ICC clients (and potentially eligible study participants) in each of the 7 sites. Overall as of June 2019, 6,590 HCV antibody positive clients have been registered across the 7 ICCs. Additionally, ICCs register a median of 35 new clients per month.

Table 10.1. Description of current clients in 7 ICCs across India

	Northeastern India		Northern India			Central India	
	Aizawl	Churachandpur	Amritsar	Ludhiana	New Delhi	Bilaspur	Kanpur
Clients (N)	2,055	837	1,573	3,430	910	1,569	919
Median age	28	34	28	26	27	27	34
% female	14.2	15.0	5.1	9.5	1.7	6.2	1.0
% on OAT	32.7	55.5	60.2	74.4	25.2	53.2	0
% inject past 6 mo	80.0	65.3	82.7	52.0	99.3	93.3	100
HCV antibody + (N)	1,113	409	1,098	2,014	566	838	552

10.1 Inclusion/Exclusion Criteria

10.1.1. Participant inclusion criteria

Participants must meet all of the following criteria to be included in the trial.

1. Registered for care at an ICC in one of the 7 field sites.

2. At least 18 years of age

3. History of injection drug use by self-report

4. Active HCV infection confirmed by a detectable HCV RNA by PCR (HCV RNA ≥ 30 IU/ml) within 90 days prior to study entry. HCV RNA will be measured by FDA-approved tests for quantifying HCV RNA at local laboratories that operate in accordance with Good Clinical Laboratory Practices (GCLP) and participate in appropriate external quality assurance programs. The YRGCARE laboratory, where the majority of testing will be done, uses the Abbott real time HCV RNA assay.

5. Liver disease stage defined as non-cirrhotic or compensated cirrhotic (metric/diagnostic criteria used for fibrosis staging) within 90 days prior to study entry as listed below:

FIB-4 <3.25 corresponding to no cirrhosis

OR

FIB-4 ≥3.25 AND Child-Turcotte-Pugh (CTP) Score ≤6 indicating CTP Class A corresponding to compensated cirrhosis.

NOTE: Individuals with decompensated cirrhosis will be excluded and referred to nearby medical gastroenterology centers where specialized treatment is available.

6. Eligible for HCV treatment (using standard eligibility criteria as per Indian National Association for the Study of Liver Disease [INASL] guidelines)
    i. Albumin >3.0 g/dL
    ii. Hemoglobin >8.0 g/dL for women; >9.0 g/dL for men
    iii. Platelet count >50,000/mm^3
    iv. Calculated creatinine clearance (CrCl) using Cockcroft-Gault method >30 mL/min
    v. Aspartate aminotransferase (AST/SGOT) <10 times the upper limit of the normal range (ULN)
    vi. Alanine aminotransferase (ALT/SGPT) <10 times the ULN
    vii. Total bilirubin <1.5 times the ULN for participants not on atazanavir (ATV) and <3 times the ULN for participants on ATV
    viii. International normalized ratio (INR) <1.5 times the ULN

7. Life expectancy greater than 1 year (as determined by study clinician)

8. Willing to initiate HCV treatment

9. Agree to be randomized to an adherence support strategy and willingness to be contacted by study staff

10. Ability and willingness to provide written informed consent

11. Female participants of reproductive potential (defined as women who have not been post-menopausal for at least 24 consecutive months, i.e., who have had menses within the preceding 24 months, or women who have not undergone surgical sterilization, specifically hysterectomy and/or bilateral oophorectomy or bilateral salpingectomy) must have a negative serum or urine pregnancy test within 48 hours prior to study entry by an approved laboratory that has Good Laboratory Practices certification or its equivalent, or using a point-of-care (POC) test. The serum, urine or POC pregnancy test must have a sensitivity of at least 25 mIU/mL.

12. All female participants of reproductive potential must agree not to participate in a conception process (e.g., active attempt to become pregnant or to impregnate, sperm donate, in vitro fertilization,) while on study treatment and for 6 weeks after stopping protocol-specified medication.

13. When participating in sexual activity that could lead to pregnancy, all female participants of reproductive potential must agree to use at least one reliable form of contraceptive while receiving protocol-specified medication, and for 6 weeks after stopping the medication. Such methods include:

- Condoms with or without a spermicidal agent
- Diaphragm or cervical cap with or without spermicidal agent
- Intrauterine device (IUD)
- Hormone-based contraceptive
- Tubal ligation

14. Female participants who are not of reproductive potential (women who have been post-menopausal for at least 24 consecutive months or have undergone hysterectomy and/or bilateral oophorectomy) are eligible without requiring the use of contraceptives. Male participants do not need to provide information on their female partner's reproductive potential.

All laboratory-based screening criteria must be measured within 90 days of the Entry Visit into the Trial with the exception of a pregnancy test for women which must be conducted 48 hours prior to study entry.

10.1.2. Participant exclusion criteria

Participants meeting any of the following criteria will be excluded from study participation.

1. Psychologically unfit to provide written informed consent

2. Planning to migrate within the next six months

3. Known allergy/sensitivity or any hypersensitivity to components of study drug(s) or their formulation.

4. Acute or serious illness requiring systemic treatment and/or hospitalization within 30 days prior to study entry.

5. In HIV positive participants, presence of active or acute AIDS-defining opportunistic infections within 30 days prior to study entry.

   NOTE: AIDS-defining opportunistic infections as defined by the Centers for Disease Control and Prevention (CDC) found in the following document: http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm

6. Use of prohibited medications within the past 14 days prior to study entry (please refer to **Section 11.2.6** for the list of prohibited medications).

7. Evidence of decompensated liver disease on clinical exam

8. Evidence of active tuberculosis

9. Evidence of chronic hepatitis B infection (HBsAg positive)

10. Currently on HCV treatment

11. Prior history of DAA-based HCV treatment

12. Confirmed active SARS CoV-2 infection or suspected active SARS CoV-2 infection at enrollment

13. Currently nursing (breastfeeding)

10.1.3. Co-enrollment criteria

HIV positive participants may be co-enrolled in the “ICC+ Study: Strategies to improve the HIV care continuum in key populations in India [DA041034].” Co-enrollment does not require permission from anyone on the protocol committee. Special attention should be paid to the timing of blood draws such that there is at least 2 weeks between blood draws for the two studies.

For co-enrollment in any other protocol, site clinicians should first check with the study Principal Investigators (PIs).

10.2 Recruitment Process

ICC Site Coordinators will be responsible for overseeing recruitment activities. Participants will be recruited primarily from the existing ICC client population. However, outreach staff will continually conduct outreach activities and community meetings to bring new clients into the ICCs. Currently, there are 6,590 HCV antibody positive ICC clients who are potentially eligible for enrollment (**Table 10.1**).

The ICC Site Coordinators will inform all existing ICC clients about the availability of free HCV testing and treatment in the ICCs. As part of the standard of care in the ICCs, all new clients who register at the ICCs will be offered free rapid HCV antibody testing with same-day delivery of results. Those who test positive will receive a blood draw for HCV RNA testing to determine active HCV infection, additional safety laboratory testing and brief clinical assessments to assess HCV treatment eligibility. Existing clients who have previously tested HCV antibody positive in the ICCs will also be informed about the availability of HCV treatment in the ICCs and invited to receive the HCV treatment eligibility assessments, if they desire. All of these assessments to determine HCV treatment eligibility (including the HCV RNA testing, safety laboratory testing and clinical assessments) will be done as part of the standard of care.

All existing ICC clients with evidence of active infection who are potentially eligible for HCV treatment will be invited to participate in the trial by the Study Site Coordinator and referred to the Study Nurse for further screening.

Based on client volume in each of these sites over the past year and HCV antibody prevalence, it is assumed that approximately 100 persons will be recruited per month (assuming that enrollment will begin in Year 2 [quarter 1] of the study). Meeting recruitment will require an average of 15-20 participants enrolled per site/month with slightly lower accrual rates in the first three months (5-8 per month).

10.3 Participant Retention

Standard retention measures will be used to ensure that participants adhere to their medication pick up visits and study visits both while on treatment and posttreatment.

Detailed locator/contact information will be collected/updated in the EHR at the time of enrollment including information on mobile phone number, alternate phone numbers, home address, hangout locations (injection venues), and addresses and phone numbers of two to three contacts. Each client will specifically be asked whether ICC staff may contact these individuals regarding appointment reminders.

For study visits (SVR evaluation visit and post-treatment follow-up visits), Site Coordinators will generate weekly reports to identify clients who are due for study visits over the next two weeks.

Once a visit is missed, outreach workers will make at least three attempts to contact participants using different approaches and different times of the day. The first attempt will be via their mobile phone. Additional attempts should include a visit to their home and/or other designated locations and/or contacts and hang out locations as needed. Outreach staff will continue to contact participants for up to one month after the missed study visit.

All tracking attempts (including the results of each attempt) will be recorded in the EHR.

Instances of migration will be documented.

Information on death and cause (via verbal autopsy) will be recorded where available.

Participants will continue to be tracked even if they miss post-treatment follow-up visits until documentation of death or migration.

11. INTERVENTIONS

11.1 Behavioral Intervention(s)

The current standard of care in India is 4-weekly dispensation of medication over a 12-week period with brief adherence counseling. Not all states in India have free HCV treatment programs but where programs are available, treatment is being delivered from government hospitals. In states where free treatment programs do not exist, treatment is available at government centers and private hospitals but individuals have to pay all costs out of pocket. The three interventions target medication adherence during HCV treatment, all providing a level of care higher than the current standard in India - delivery from community-based PWID-friendly clinics.

Three arms will be compared: Arm 1) low intensity support; Arm 2) medium intensity support; and Arm 3) high intensity support (**Table 11.1**). These interventions involve a combination of standard of care procedures, patient navigation and directly observed therapy (DOT). Interventions will be delivered by nurses and study patient navigators (PN) who may or may not be peers.

All staff delivering the intervention will complete an HCV training program prior to any interactions with study participants. Interventions target individual barriers to mediation adherence within the

context of a structural intervention for HCV treatment (integration of HCV treatment within already existing HIV and harm reduction services).

Additional details regarding all of these interventions can be found in the **Study Manual of Operations (MOP)**.

11.1.1. Arm 1. Low intensity HCV treatment adherence support

11.1.1.1. Arm 1. Medication delivery. The standard of care in India is 4-weekly dispensation of medication at three appointments over a 12-week period. Participants assigned to this Arm will have their medications dispensed as per this standard of care. At the Study Entry Visit, participants will receive their first bottle of medication. During treatment, participants in this Arm will receive their study medications 1) at their home (delivered by a PN); 2) a chosen location (delivered by a PN); or 3) at the ICC. Medication drop-off/pick up will be required two additional times after treatment initiation (five times for those receiving 24 weeks of treatment) for refills. Medication drop-off/pick up will be scheduled a few days before the 28-day supply of medication is set to run out. The decision as to the mode for medication drop-off/pickup will be based on precautions in place for COVID-19 which are designed to maximize participant/staff safety.

11.1.1.2. Arm 1. Adherence Support. Participants in this arm will receive standard adherence support. The standard adherence support in India entails general adherence counseling and tracking for missed medication refill pick-ups.

At the Entry Visit, the study nurse and a counselor will provide standard counseling on HCV treatment, the importance of treatment adherence and risks of reinfection. The counseling protocol which includes pictorial guides is based on a combination of what is used in India and has been developed for PWID in the US (See **Study MOP** for details). This standard counseling will be repeated at each of the additional medication pick-up/drop-off visits. Counseling will happen either 1) over the phone; or 2) in person depending on precautions in place for COVID-19.

Participants in this arm will be provided with a phone number to call with any problems related to study treatment and/or side effects as needed.

11.1.1.3. Arm 1. Linkage to other services. The **Resources List** that will be maintained at each ICC will provide a list of resources at the ICC (e.g., OAT) and within each city (e.g., government social protection schemes). Participants in this arm will have access to all ICC services including testing and care for HIV, STI management, TB testing and linkage, counseling, condoms, OAT, SSP and will be provided with other service referrals as needed.

While participants in this arm will not have a specific PN assigned to them, PN at the ICC can help to facilitate linkages/referrals as needed.

The following services are available at the ICCs:

HIV testing and counseling: HIV testing and counseling is provided in all ICCs via three rapid tests as per the standard of care in India. Confirmatory testing which is required by government of India is done in some ICCs and where not available, PN accompany lab samples taken at the ICCs to government integrated counseling and testing centers for confirmatory testing.

Antiretroviral therapy: In some ICCs (e.g., Aizawl), ART is available on-site and in others, ART records are maintained at the ICC and peers accompany individuals to the government ART centers for refills or collect refills on behalf of the clients. Home-delivery of ART is available in some locations due to precautions put in place for COVID-19.

Tuberculosis management: ICCs perform standard symptom screening for TB. Those with a positive symptom screen are provided with a sputum collection container which is collected at the ICC and transported to the nearest government directly observed therapy (DOTS) center. Those who need treatment are linked to the nearest DOTS center.

Sexually transmitted infection management: As per the standard of care in India, nurses perform screening for STIs and deliver syndromic treatment. Treatment is provided by the Indian National Government and dispensed through the ICCs. Syphilis testing is also conducted on site.

Opioid agonist therapy: In each ICC, OAT is provided by the Indian National government and dispensed through the ICCs. Doses are taken in front of nurses and are observed seven days a week. Because of COVID-19, most ICCs are providing extended dosing of OAT with the majority offering 7 days of medication at a single visit.

Syringe services: Syringes are provided at nearby hotspots. When individuals need syringes, peers navigate them to the hotspots where they can receive them.

Condoms: Condoms are available freely within the ICCs

Counseling: Counselors in the ICCs have been trained in motivational interviewing. They provide individual, couples and group level counseling at the ICCs. Focused areas include treatment adherence, substance use including alcohol use, depression and other mental health comorbidity as well as disclosure issues around sexual identity and HIV status. Individuals who need additional support for alcoholism or mental health issues are referred.

Other specific services which are not available onsite and will require referral include inpatient treatment for drug and/or alcohol use, pharmacologic treatment for alcohol use, TB treatment and mental health services.

11.1.1.4. Arm 1. Participant tracking. Tracking efforts will be triggered by missed medication refill pickups. PN will generate daily reports of participant attendance to determine who has missed a refill appointment. As soon as a participant misses a refill pickup, tracking will be initiated. At least three attempts will be made to contact each participant using different approaches at different times of the day. The first attempt will be via the participants mobile phone (if the participant has a phone). Additional attempts should include a visit to the participant's home and/or hangout locations as specified in the locator form and as needed unless there is evidence of death or migration.

PN will continue to attempt to contact participants up to 2 weeks after the medication refill appointment is missed. After 2 weeks, tracking attempts for medication refill appointments can be ceased. However, participants will still be tracked for SVR evaluation visit.

11.1.2. Arm 2. Medium intensity HCV treatment adherence support

11.1.2.1. Arm 2. Medication delivery. The standard of care in India is 4-weekly dispensation of medication at three appointments over a 12-week period. Participants assigned to this Arm will have their medications dispensed as per this standard of care. At the Study Entry Visit, participants will receive their first bottle of medication. During treatment, participants in this Arm will receive their study medications 1) at their home (delivered by a PN); 2) at a chosen location (delivered by a PN); or 3) at the ICC. Medication drop-off/pick-up will be required two additional times after treatment initiation (five times for those receiving 24 weeks of treatment for refills. Medication drop-off/pick up will be scheduled a few days before the 28 day supply of medication is set to run out. The decision as to the mode for medication drop-off/pick up will be based on precautions in place for COVID-19 which are designed to maximize participant/staff safety.

11.1.2.2. Arm 2. Adherence support. Participants in this arm will receive tailored PN adherence support that seeks to address individual barriers and leverage facilitators to adherence to treatment and medication refill appointments.

A PN is a staff member who is knowledgeable about local HIV care, substance use, harm reduction and mental health services (e.g., government social protection schemes) such that they can facilitate linkage to other services that are needed and can promote adherence to hepatitis C treatment. PN will also dually serve as counselors as needed.

At the Study Entry visit, each participant in this arm will be assigned to a specific PN who will support him/her through the entire treatment process to the SVR visit. At the Study Entry Visit, PNs will meet with participants and complete the electronic **Patient Navigation Form** to collect information on perceived/actual barriers and facilitators to taking HCV medication. This form includes information on 1) basic demographics; 2) employment and income; 3) mental health issues; 4) ongoing drug and alcohol use and engagement with substance use services; 5) housing and incarceration; 6) mode of transportation to medication refill/study visits; 7) HIV status and engagement with HIV care; 8) family and social support. This form will allow the PN to document the participant's level of engagement with needed HIV and substance use services as well as service needs. This includes services at the ICCs as well as outside referrals for mental health services and social protections schemes as available in India.

After completing the electronic **Patient Navigation Form**, the PN in collaboration with the participant will complete the electronic **Hepatitis C Care Plan.** The goal of the **Hepatitis C Care Plan** will be to formulate a plan to overcome specific barriers identified in the **Patient Navigation Form**. This plan will include facilitation of referrals both within and outside of the ICC, identification of additional support persons needed and counseling needs. The form will be completed at the first point of contact between the PN and the participant but will allow for continual updating throughout treatment. The form will collect information on the scheduled medication pick-up/drop-offs, the referrals both inside and outside the ICC that are needed and made. And finally, the form will include a set of goals set by the PN and the participant. In addition, the participant and the PN will decide on the frequency (e.g., daily, weekly including time of day) and mode of contact (e.g., SMS, WhatsApp, phone call, field contact) from a menu of options. This frequency will be documented on the **Patient Navigation Form**. At a minimum, the PN must make contact every two weeks (minimum of 6 contacts during 12 weeks of treatment) but there is room for flexibility depending on participant needs. During these contacts, the PN will provide medication adherence support/reminders as needed, counseling as needed and updates on service linkages.

At a minimum, there will be three additional face-to-face contacts (either at the participant's home or at the ICC) between the PN and each participant. These will occur at each medication drop-off/pick-up visit and the end of treatment visit. During these visits, the **Hepatitis C Care Plan** will be modified as needed. Throughout the course of therapy, either at the study visit or in between visits, the PN may modify the frequency and mode of contact during the course of the medication to respond to difficulties or success.

11.1.2.3. Arm 2. Linkage to other services. The **Resources List** that will be maintained at each ICC will provide a list of resources at the ICC (e.g., OAT) and within each city (e.g., government social protection schemes). Participants in this arm will have access to all ICC services including testing and care for HIV, STI management, TB testing and linkage, counseling, condoms, OAT, SSP and will be provided with other service referrals as needed.

At this Entry Visit, the PN will make the appropriate referrals and document them on the **Hepatitis C Care Plan**.

At each follow-up visit, additional needs will be identified and referrals will be made as needed. All referrals made will be documented in the **Hepatitis C Care Plan.**

11.1.2.4. Arm 2. Participant tracking. PNs will maintain detailed **Contact Logs** which will track each call/contact. In addition, all participants in this arm will receive a reminder phone call/text two days before a medication pickup/drop-off is due. For clients who do not have mobile phone numbers, PN may need to physically visit hang out locations and/or residences in order to physically accompany individuals to medication refill visits. Clients who miss refills will be tracked using the same process as Arm 1.

No more than 20 participants at a time will be assigned to a single PN.

11.1.3 Arm 3. High intensity HCV treatment adherence support

11.1.3.1. Arm 3. Medication delivery. All participants in this Arm will receive some form of directly observed therapy (DOT) with a maximum amount of flexibility allowed to account for changing mobility restrictions. A minimum of 1 dose per week will be observed for all participants but up to 7 doses can be observed depending on need. Participants will receive either ICC-based DOT, field-based DOT or some combination.

For participants who are receiving 7 days of DOT in the ICC, pills will be maintained at the ICC. For these participants receiving 7 days of medication at the ICC, the PN/Nurse will first scan the participant's biometric to determine the study ID. The participant's pillbox will be retrieved and then the medication dose delivered by either the Study Nurse or a PN. Each time a dose is delivered in the field, it will be entered into an electronic **DOT Log**.

Participants who receive DOT 1-6 days/week in the ICC or 1-6 days in another location will receive a week's worth of medication to keep with them. This will contain all of the doses of medication including those that will and will not be observed. When the participant comes to the ICC or meets with outreach workers at the identified location, they will bring their medication container and the outreach worker will bring a laptop and a biometric device. Once the participant's identity is confirmed, the dose will be taken and recorded in the electronic **DOT Log**.

For participants receiving field-based DOT, communication between the PN and the participant will take place using mobile phones, typically WhatsApp. The PN and the participant will decide on a location to meet the participant and will communicate about the time. The goal will be to maintain some consistency in schedule but the protocol will allow for flexibility.

Regardless of location or frequency of DOT, each participant will receive 3 emergency take home doses. Use of take home doses should be documented in the EHR. As emergency doses are used, they will be replenished.

11.1.3.2. Arm 3. Adherence Support. At the Study Entry Visit, all participants randomized to this arm will be assigned to a PN. The PN will meet with each participant at this visit to fill out the electronic **Patient Navigation Form** to collect information to decide on support and service referrals needed as well as the frequency of DOT. This form will include information on 1) general demographics; 2) income and education; 3) mental health issues; 4) ongoing drug and alcohol use and engagement with substance use services; 5) housing and incarceration; 6) mode of transportation to medication refill/study visits; 7) HIV status and engagement with HIV care; and 8) family and social support.

Like participants in Arm 2, the PN will fill out a **Hepatitis C Care Plan**. The purpose of this plan is similar to what it is for Arm 2 but with a focus on identifying additional barriers to treatment adherence and service linkages needed.

In addition, for this arm, the PN and the Nurse will be provided with a **DOT Guide** that is used as a guide to determine the frequency and site of DOT. This will include recommendations based on the barriers and facilitators identified on the **Patient Navigation Form**. For example, if participants reside at a distant location and do not have transportation, field-based DOT will be recommended. If participants are receiving daily OAT at the ICC, ICC-based DOT will be recommended. The mode/frequency of DOT will be recorded on the **HCV Care Plan**. A protocol will be in place to modify the frequency of DOT both for participants who are doing well (to become less frequent) and for participants who are not doing well (to become more frequent). The decision to modify the frequency of DOT will be based on a review of the adherence data at 4 and 8 weeks and joint discussion between the nurse, PN, and participant. Only those participants who have >95% adherence over 4 weeks will be able to reduce the frequency of DOT but the minimum number of contacts will remain at 1 per week. If there is a change in frequency of DOT, it must be noted on the **HCV Care Plan**.

Possible options for DOT include:

- DOT in conjunction with daily (or less frequent) OAT with buprenorphine. The schedule of HCV DOT should match the schedule of OAT DOT
- DOT at the ICC for participants not on OAT.
- Field-based DOT where medication will be delivered by outreach worker at a location of the participant's choosing (home, work, hangout location) 1-7 times/week.

11.1.3.3. Arm 3. Linkage to other services. The **Resources List** that will be maintained at each ICC will provide a list of resources at the ICC (e.g., OAT) and within each city (e.g., government social protection schemes). Participants in this arm will have access to all ICC services including testing and care for HIV, STI management, TB testing and linkage, counseling, condoms, OAT, SSP and will be provided with other service referrals as needed.

At this Entry Visit, the PN will make the appropriate referrals and document them on the **Hepatitis C Care Plan**.

At each follow-up visit, additional needs will be identified and referrals will be made as needed. All referrals made will be documented in the **Hepatitis C Care Plan.**

11.1.3.4. Arm 3. Participant tracking. Participants who miss an in-clinic dose will be tracked in real-time. PN will attempt to reach the participant by phone and/or by visiting their home or other designated location. If needed, a single dose can be delivered in the field.

If a field-based dose is missed, PN will attempt to reach the participant by phone and/or by visiting their home and/or reaching out to contacts/visiting hang out locations.

Table 11.1. Summary of intervention and standard packages of services by study arm

	Arm 1: Low Intensity	Arm 2: Medium Intensity	Arm 3: High Intensity
Medication Delivery			
4 weekly dispensation	X	X	
Weekly dispensation			X
Observed doses (1-7 doses/week)			X
Adherence Support			
Standard adherence counseling at treatment initiation	X	X	X
Adherence counseling at medication pick-up visits	X	X	X
Phone number provided for support as needed	X	X	X
Tailored PN support			
Creation/implementation of hepatitis C care plan		X	X
Regular contact during treatment (minimum of once/ 2 weeks)		X	X
Medication reminders (as needed)		X	
Directly observed doses			X
Linkage to Other Services			
Access to all ICC services (HIV testing with linkage to treatment, STI management, TB testing and linkage, counseling, condoms, OAT, SSP	X	X	X
Facilitated linkage to services available within the ICC and outside of the ICC	X	X	X
Participant Tracking			
Phone/in person tracking for missed medication pick-ups initiated within one day of a missed medication pickup – at least 3 attempts	X	X	

11.1.4. Staffing/Training of personnel delivering intervention

11.1.4.1. Number of staff supporting program. HCV treatment adherence support (and treatment) will be primarily supported by a part-time physician, a nurse, a counselor and 3-5 PN at each site. At each site we will start with 3 PN assuming that each PN can handle approximately 20 clients at a time. We anticipate having a maximum of 60 persons on treatment at an ICC at any given time. Assuming that all participants in Arms 2 and 3 will be matched to an individual PN and that participants in Arm 1 may have PN support for some referrals (without being explicitly matched to a PN), we assume that approximately 40-45 will need intensive PN support at a given time. Thus, 3 PN should be sufficient at any given time in each ICC. However, if the volume exceeds this number in any given site, additional PN will be provided to the site.

11.1.4.2. Intensive training prior to program start. A tailored version of a Johns Hopkins program, Sharing the Cure, will be used to train all personnel that will support HCV treatment. Nurses, counselors, PN and physicians will participate in a 3-day virtual training. This will include a 1-day conference on HCV diagnosis and treatment with didactic training and small group sessions. The training will be led by Sharing the Cure program faculty and clinicians managing HCV in India. The next two days will involve virtual shadowing of clinicians at YRGCARE.

11.1.4.3. Training support during the program. For one year after the intensive training, teams will participate in bi-monthly video calls via Zoom. Calls will include Drs. Solomon and Amrose, a member of Sharing the Cure and ICC teams. Each session will include updated treatment information, case studies and updates on barriers faced at the sites. The latter six months of the training will occur while treatment is being rolled out in the ICCs so questions can be shared in real-time.

11.1.4.4. Electronic support. We will form a “WhatsApp” group for clinicians and nurses that will continue after training. WhatsApp, a free messaging application with encryption capabilities, has >200 million users in India. A commonly used feature is multi-user groups allowing real-time exchange of messages including attachments (e.g., treatment guidelines) across members; a group can contain up to 256 persons. This group will include core members (Drs. Solomon, Amrose, Balakrishnan) for anonymous case discussions. ICC staff can post questions on this group that will be responded to by the core team. No personal health information will be shared.

11.1.4.4. Fidelity assessments. There will be a formal written and case-based assessment after the initial intensive training; staff will be certified accordingly. There will be an additional assessment one year after the training.

11.2 Study Treatment

As part of the background, hepatitis C treatment will be provided as the standard of care in the ICCs according to the INASL guidelines. Medication will be provided by the study but is not part of the experimental condition being compared. The regimens used will not differ by arm.

11.2.1. Regimens

For participants without HIV infection and who are HIV-infected but not on an efavirenz containing regimen, the treatment will be once-daily generic oral fixed-dose combination of sofosbuvir/ velpatasvir (SOF/VEL) containing 400 mg of SOF and 100mg of VEL. Treatment duration will be 12 weeks taken orally with or without food. If a participant is co-infected with HIV and on an efavirenz containing regimen they will have the option to switch to a non-EFV containing regimen (e.g., DTG) for at least two weeks prior to initiation of DAA therapy with SOF/VEL. The government of India is modifying their guidelines and a combination of tenofovir/emtricitabine/dolutegravir TDF/FTC/DTG will be the preferred first-line regimen. The government is expected to roll-out this combination in December 2019 ahead of the initiation of this trial.

If the participant is unable to modify the ART regimen to a non-EFV containing regimen, they will receive once-daily generic oral fixed-dose combination of sofosbuvir/daclatasvir (SOF/DAC) including 400 mg of SOF and 60 mg of DAC (an additional 30 mg pill of DAC will be dispensed as

required). Treatment duration for this group will be guided by the presence/absence of compensated cirrhosis and genotype. For those with genotype 3 infection and compensated cirrhosis, treatment duration will be 24 weeks. For all others, treatment duration will be 12 weeks. All treatment will be oral with or without food.

For Arms 1 and 2, the Study Nurse will observe the first dose being taken by the participant upon completion of all entry evaluations. Participants will receive only one bottle of study product at a time.

Participants in Arms 1 and 2 will be scheduled to have a scheduled pick-up/drop off for the next bottle of study medication three days prior to when their last pill is due from that bottle. Participants will be asked to retain empty study bottles and return them to the study staff.

For Arm 3, study staff will observe the first dose being taken by the participant upon completion of all study entry evaluations. Over the remaining course of therapy, participants will be observed by study staff for 1-7 doses per week (see **Section 11.1.3** for details). Pill boxes will be used to distribute medications to these participants. The pill boxes will be refilled each week. Each participant will also be given three emergency doses in case a DOT appointment is missed. These three rescue doses will also be replenished as used.

11.2.2. Study product supply and accountability

11.2.2.1. Overview of pharmacy plan. In each of the 7 cities, a stand-alone existing venue/free-standing pharmacy will be identified that is a proximate to the ICC. All sites will be modified as needed to meet DAIDS requirements and store study product. Specifically, this will include continuous temperature monitoring with recording of minimal and maximum temperatures reached over a period of time as well as manual temperature monitoring at least once/day. Study medications will be managed at the central YRGCARE pharmacy in Chennai, shipped to the local pharmacy once/month and dispensed through the ICCs. A chain of custody form will track the medication from the point of shipment to transfer to the study team and finally when the medication is handed over to the participant.

11.2.2.1. Study product acquisition/distribution. The fixed dose combination (FDC) of SOF/VEL, SOF/DAC and 30 mg tablet of DAC will be purchased from Mylan Pharmaceuticals. As of 27 October 2020, SOF/VEL and SOF/DAC produced by Mylan Pharmaceuticals have been prequalified by WHO. The 30/60 mg tablet of DAC produced by Mylan Pharmaceuticals was WHO prequalified as of 15 May 2019. All are currently approved for use in India by the Drug Controller General India.

The central study pharmacy will be located within the YRGCARE premises in Chennai – medication will be shipped to each site on a monthly basis according to participant recruitment at the sites.

Currently, the cost for purchasing a 12-week course of SOF/VEL or SOF/DAC is USD 150-200. There have been no reports of diversion of medications either from cities/states where there are free HCV treatment programs in place nor from research studies involving PWID. In order to avoid diversion, participants will not be given study medications in the original labeled bottles. Medications will either be in new bottles labeled with study information or pillboxes depending on the Arm assignment.

Both SOF/VEL and the alternate regimen SOF/DAC will be purchased through the study and provided to participants. However, in some sites, some medications will be provided by local government/hepatitis C treatment programs free of charge. In these cases, medications (SOF/VEL and SOF/DAC) would be acquired by the Site Pharmacist and stored at the Site Pharmacy along with the medications purchased for the study and dispensed in exactly the same manner as medications purchased for the study.

When a study participant initiates HCV treatment through the trial at one of the community-based centers, contact will be made with the study pharmacy. The study medications will be packaged by a study team member under the supervision of the local pharmacist into the required containers (bottles/packs for Arms 1 and 2 and pillboxes for Arm 3). The medication label will comply with local Indian guidelines. A peer navigator/logistics assistant will transport a one month supply of medication for participants in Arms 1 and 2 from the study pharmacy to the ICC/location for drop-off where each participant will receive the medication from the study nurse or a peer navigator. When the participant is due for a refill, the logistics assistant will pick up the next supply of medication on the morning when the participant is due for that refill. If the participant cannot be reached for pick-up/drop-off of a refill, the medication will be returned to the pharmacy and picked up again the following morning such that it will be stored for a maximum of 12 hours on site at the ICC. For arm 3, a one-week supply of medication (in a pillbox) will be picked up from the pharmacy and handed over to the participant as per the frequency of DOT assigned.

11.2.2.2. Study product accountability. The Site Pharmacist will be required to maintain complete records of all study products received from the Central Pharmacy and subsequently dispensed. First the medication will be labeled and handed off to the site personnel for transport to the ICC/participant. Chain of custody will be documented from the point of shipping from the Central Pharmacy to study staff to the final point when medications are handed over to a study participant. At this point, biometric identification will be used to document receipt of the medication by the participant.

All unused study products must be returned to the Central Pharmacy after the study is completed or terminated. The Central Study Pharmacist will follow appropriate protocols for destruction of unused study products.

Medications provided by local government/hepatitis C treatment programs will be logged and tracked in a separate system. The Site Pharmacist will follow appropriate protocols for destruction of unused product.

11.2.3. Assessment of participant adherence with study treatment

The behavioral interventions being evaluated target participant treatment adherence.

At each on treatment study visit (every 4 weeks for 12 weeks [or 24 weeks] total), participants will be asked to self-report adherence using a visual analogue scale.

Participants will be asked to return their empty pill bottles at which time the number of pills remaining will be counted.

11.2.4. Concomitant medications and procedures

Whenever a concomitant medication or study agent is initiated or a dose changed, investigators will review the concomitant medication's and study agent's most recent package insert, Investigator's Brochure, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

Additional drug information may be found on the ACTG Precautionary and Prohibited Medications Database located at: http://tprc.pharm.buffalo.edu/home/di_search/.

11.2.5. Permitted medications and procedures

For Sofosbuvir/Velpatasvir, no clinically significant drug interactions have been observed with the following medications which are thus permitted.

- EPCLUSA®: atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, dolutegravir, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, raltegravir, or rilpivirine
- Sofosbuvir: ethinyl estradiol/norgestimate, methadone, or tacrolimus
- Velpatasvir: ethinyl estradiol/norgestimate, ketoconazole, or pravastatin.

For Sofosbuvir/Daclatasvir, no clinically significant drug interactions have been observed with the following medications which are thus permitted.

- Sofosbuvir: cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, methadone, or rilpivirine**,** ethinyl estradiol/norgestimate or tacrolimus
- Daclatasvir: cyclosporine, darunavir (with ritonavir), dolutegravir, escitalopram, ethinyl estradiol/norgestimate, lopinavir (with ritonavir), methadone, midazolam, tacrolimus, or tenofovir No dosage adjustment for daclatasvir is necessary with darunavir/cobicistat or moderate CYP3A inhibitors, including atazanavir (unboosted), fosamprenavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, or verapamil.

11.2.6. Prohibited medications and procedures

The following medications are prohibited with Sofosbuvir/Velpatasvir:

- Acid Reducing Agents: antacids (e.g., aluminum and magnesium hydroxide), proton pump inhibitors (e.g., omeprazole), H2-receptor antagonists (e.g., famotidine),
- Antiarrhythmics: amiodarone, digoxin
- Anticancers: topotecan
- Anticonvulsants: carbamazepine, phenytoin, phenobarbital, oxcarbazepine
- Antimycobacterials: rifabutin, rifampin, rifapentine
- HIV Antiretrovirals: efavirenz (velpatasvir interaction), etravirine, Regimens containing tipranavir/ritonavir (sofosbuvir interaction)
- Herbal Supplements: St. John's wort (Hypericum perforatum)
- HMG-CoA Reductase Inhibitors: rosuvastatin, atorvastatin
- Ribavirin

The following medications are prohibited with Sofosbuvir/Daclatasvir:

- Antiarrhythmics: amiodarone, digoxin

- Anticonvulsants: carbamazepine, phenytoin, phenobarbital, oxcarbazepine
- Antimycobacterials: rifabutin, rifampin, rifapentine
- HIV Antiretrovirals: etravirine, Regimens containing atazanavir/ritonavir, indinavir, saquinavir, nelfinavir (daclatasvir interaction); Regimens containing tipranavir/ritonavir (sofosbuvir interaction)
- Herbal Supplements: St. John's wort (Hypericum perforatum)
- HMG-CoA Reductase Inhibitors: rosuvastatin, atorvastatin

11.2.6. Treatment delivery

All treatment will be provided in the ICCs as per the standard of care in India. Fibrosis-4 score (FIB-4),[91] which has been validated in India,[92] and Child Turcotte Pugh's (CTP) score will be used to determine fibrosis stage and assess cirrhosis stage. Participants with minimal disease will be managed by nurses, but all prescriptions will be made by physicians as required by Indian law. Those with FIB-4 ≥3.25 or cirrhosis on clinical exam will require consultation with the YRGCARE clinic and/or medical gastroenterology to rule out decompensated cirrhosis. Clients with Childs Turcotte Pugh B or C (decompensated) cirrhosis will be excluded from the trial and referred to the medical gastroenterologist for management of their cirrhosis. Those with compensated cirrhosis will still receive treatment at the ICC with guidance from specialists as needed.

As described in **12.3.9**, minimal laboratory monitoring will be used.

12. STUDY PROCEDURES/EVALUATIONS

12.1 Schedule of Procedures/Evaluations

Table 12.1. Schedule of Procedures/Evaluations

	Pretreatment	On Treatment				Post treatment	
	Screening	Entry / Week 0	Week 4	Week 8	Week 12	Week 24 (SVR 12 evaluation)*	Weeks 48, 72, 96, 120, 144, 168, 192, 216)**
Documentation of active HCV infection, HCV RNA+ [EHR review]	X					X	
Documentation of HIV status [EHR review]	X						
Calculated FIB-4 score [EHR review]	X					X	
Documentation of Cirrhosis Status [EHR review]	X					X	
Calculated CTP Score, if cirrhotic [EHR review]	X					X	
Brief medical history	X						
Medication history	X	X	X	X	X	X	
Clinical evaluation (EHR review, exam, vital signs)	X					X	
Complete blood count [EHR review]	X					X	
Liver function tests [EHR review]	X					X	
Renal function tests [EHR review]	X					X	
Calculated creatinine clearance [EHR review]	X					X	
INR [EHR review]	X					X	
Pregnancy test (women)	X	X	X (if pregnancy is suspected)			X	
HBsAg testing [EHR review]	X					X	
CD4 (if HIV antibody positive) [EHR review]	X						
Stored Plasma/Serum specimen		X			X	X	X
Screening Questionnaire	Z						

	Pretreatment	On Treatment				Post treatment	
	Screening	Entry / Week 0	Week 4	Week 8	Week 12	Week 24 (SVR 12 evaluation)*	Weeks 48, 72, 96, 120, 144, 168, 192, 216)**
Written informed consent	Z/X						
Register/verify Biometric	X	X	X	X	X	X	X
Demographics questionnaire		Z				Z	Z
Social / family support questionnaire		Z					
Quality of life questionnaire		Z				Z	Z
Substance use and risk behavior questionnaire		Z	Z	Z	Z	Z	Z
Contact/Locator information	X	Z	Z	Z	Z	Z	Z
Randomization		X					
Pregnancy prevention counseling	X	X	Z	Z	Z		
Adherence counseling		X	Z	Z			
Cirrhosis/liver health counseling		X			Z	Z	Z
HCV risk reduction counseling		X	Z	Z	Z	Z	Z
Assignment to PN (Arm 2 and 3 only)		X					
Meet with PN to complete Hepatitis C Care Plan (Arms 2 and 3) and DOT location/schedule (Arm 3 only)		X					
Medication dose observed***		X	X	X			
Adherence assessment			X	X	X		
HCV core antigen testing****							X

X indicates that the data collection/assessment must take place in the ICC: Y indicates that this data collection may be collected at the ICC, at a participant's home or at an alternative location depending on precautions in place for COVID-19; Z indicates that the data collection may take place at the ICC or over the phone depending on precautions in place for COVID-19
*For participants who receive 24 weeks of therapy, the SVR visit will take place at 36 weeks
**For participants who receive 24 weeks of therapy, these visits will take place at weeks 60, 84, 108, 132, 156, 180, 204, 228
***Additional doses will be observed for Arm 3 (36 to 84 for those receiving 12 weeks of treatment and 72 to 168 for those receiving 24 weeks)
****Only assessed on participants who achieve HCV cure

12.2 Timing of evaluations

12.2.1. Screening evaluations

Screening evaluations must occur prior to the participant starting any study medications, treatments or interventions. Screening evaluations can take place any time when a potentially eligible participant visits the ICC after s/he has had an initial evaluation for HCV treatment eligibility. Evaluation for HCV treatment eligibility will be completed as part of the standard of care in the ICCs. All laboratory results to determine HCV treatment eligibility will be documented in the EHR and will be abstracted as part of the Screening process. Screening assessment may occur over the course of one or more visits, but must be completed within 90 days of the blood draw to ascertain laboratory parameters.

The goal of the Screening Visit is to evaluate participants with evidence of active HCV infection (HCV RNA positive) who are deemed to be potentially eligible for HCV treatment based on standard laboratory criteria. Written informed consent will be required prior to conducting the Screening assessments.

As part of the standard of care in the ICCs, HCV antibody testing will be offered to PWID clients in the 7 ICCs; however, as testing is available in other locations, we will also accept documentation of HCV antibody status from a government center or a private laboratory with appropriate certifications.

Individuals with evidence of HCV antibodies will receive additional evaluation for HCV treatment eligibility as part of the standard of care in the ICC. They will meet with a clinician in the ICC in order to further ascertain their eligibility for HCV treatment. This will include:

- Brief symptom screen for tuberculosis
- Brief clinical exam (to assess signs and symptoms of liver disease [e.g., ascites])
- Blood draw to ascertain HCV RNA status, Hepatitis B Surface Antigen (HBsAg) status, liver function tests, renal function tests, a complete blood count and HIV/CD4 status (if not available in the EHR).
- Women will receive a pregnancy test.

Laboratory tests will be valid for 90 days after their completion so eligible participants must complete the Entry Visit within this time period. Thus Screening should take place soon after the initial HCV treatment eligibility assessment is complete.

At Screening, all potentially eligible trial participants will first be asked to provide written informed consent. After consent, laboratory and clinical data relevant to treatment eligibility will be abstracted from the EHR by the study nurse to determine eligibility or HCV treatment.

All participants who have HCV RNA between 30 IU/ml and 1000 IU/ml will undergo repeat HCV RNA screening ≥14 days after the initial to confirm chronic HCV infection and treatment eligibility. A repeat detectable viremia will be considered detectable.

Persons with evidence of cirrhosis by FIB-4 and CTP will be referred to the YRGCARE clinical team and/or medical gastroenterology for further assessment. Those with compensated cirrhosis can be enrolled in the trial and managed at the ICC with consultation from medical

gastroenterology. Those with decompensated cirrhosis will not be eligible for HCV treatment at the ICC or enrollment in the trial.

All those who are eligible for HCV treatment in the ICC will undergo additional procedures for this screening visit:

- Scan biometric to record/confirm participant identity
- Administer brief questionnaire to determine additional screening criteria
- Collect contact/locator information

In addition to data being collected on participants who are eligible and enroll into the study, demographic, clinical and laboratory data will be captured for those who are not eligible and do not enroll in an electronic Case Report Form (eCRF).

While COVID-19 safety precautions are in place, in order to reduce face-to-face contact between participants and study staff, some activities will be conducted over the telephone if possible (initial review of written informed consent document, brief questionnaire and collection of contact/locator information).

12.2.2. Entry/Enrollment evaluations

Entry evaluation for most will take place on the same day as the screening. If not, the maximum time allowable is 90 days from when the laboratory testing for HCV treatment eligibility has been completed. For participants who do not want to complete entry evaluations on the same day as screening, appointments will be scheduled as soon as possible (i.e., 1-2 days).

At the Entry Visit, the Study Nurse should first administer the **Entry Visit Behavioral Survey** to inform randomization. The Entry Visit survey includes the following modules. The survey will be completed in an eCRF.

- Demographics
- Social / family support
- Quality of life
- Substance use, risk behavior and treatment

In addition, at the Entry visit, participants will undergo a laboratory draw for specimen repository storage and women of childbearing potential will have a pregnancy test.

While COVID-19 safety precautions are in place, the Entry Visit Behavioral Survey will be completed over the phone rather than face-to-face in order to reduce the risk to study staff and participants.

The following additional activities will take place at the entry visit after completion of the survey.

- Randomization (See **Section 15.5** for details): The propensity for treatment non-adherence will be determined by an algorithm (not shared with participants or site staff) and accordingly participants will be randomized to receive low, medium or high intensity treatment support. The Study Nurse will use the randomization tab in the EHR to assign the participant to the corresponding Study Arm (level of treatment support).
- Update contact/locator information

Additional activities at the Entry Visit will differ by study Arm

- Preparation for HCV treatment adherence support

  - Arm 1 - Meet with a PN to receive standard adherence counseling
  - Arm 2- - Assignment to a PN
    - PN to complete **Patient Navigation Form** to identify barriers and services needed
    - PN to complete **Hepatitis C Care Plan** including information on schedule/frequency of contact and referrals
    - PN to prepare **Contact Log**
  - Arm 3 - Assignment to a PN
    - Jointly meet with PN/Nurse to complete **Patient Navigation Form**
    - PN to complete **Hepatitis C Care Plan**
    - PN to schedule frequency/location of DOT visits
    - PN to begin **DOT Log**
- Observation of first dose (All Arms)
- Schedule next appointment/contact
  - Arm 1: 4 weeks
  - Arm 2: 4 weeks
  - Arm 3: next observed dose (next day to 7 days)

Most participants will be randomized and begin treatment within 24-48 hours of completing the screening evaluations. However, the maximum time between when laboratory testing is done in the ICC to determine HCV treatment eligibility and the entry visit is 90 days. The first dose of SOF/VEL or SOF/DAC will be observed by study personnel at the entry visit.

12.2.3. On treatment evaluations

Participants in all arms will have brief on-treatment evaluations at 4, 8 and 12 (end of treatment) weeks after the entry visit (treatment start).

A minority of participants will receive 24 weeks of treatment and so will have additional on-treatment evaluations at 16, 20 and 24 (end of treatment) weeks.

Because some of these visits include medication pickup, the goal is to conduct the visits within a +/- 2 day window. However, up to a +5 / -14 day window will be permissible for visits with medication pick up (visits outside this window are allowed if approved by study doctor).

The following assessments will be done

- Scan biometric to confirm identity
- Administer a brief survey on substance use, risk behavior and medication adherence, record answers in eCRF
- Update medication history
- Provide updated contact/locator information
- Count the pills remaining in the prior bottle
- Provide the next bottle of medication (Arms 1 and 2 only; at all except 12 week visit)
- Observe that day's dose if it has not been taken
- Draw blood for repository (Week 12 [or Week 24] visit only)
- Pregnancy test (if female and pregnancy suspected)
- Assess adverse events
- Schedule next appointment

While COVID-19 safety precautions are in place, we will attempt to complete these visits with minimal face-to-face contact and so will offer alternatives. For the on-treatment evaluations, we will complete surveys, updating of locator information and counseling over the phone. We will offer multiple options for medication refills other than pickup at the ICC including drop off to home or some other mutually agreed upon location. Prior bottles will be collected and stored for several days before pills are counted. For the end of treatment visit, surveys will be completed over the phone but an in-person visit will be preferred for the blood draw. Exceptions will be made for this in-person requirement in cases where 1) COVID-19 precautions make travel to the site challenging; and 2) participants are in rehabilitation facilities (e.g., drug detoxification programs) or cannot travel to the site for another reason.

12.2.4. SVR evaluations

SVR evaluations will be assessed on the majority of participants at week 24 (12 weeks after treatment completion). For a minority of participants who receive 24 weeks of treatment, the SVR evaluations will take place at week 36. The window for the SVR assessment visit will be -2 weeks (10 weeks after treatment completion) to 60 weeks after treatment completion (i.e., study weeks 22-72). Visits outside this window are allowed with documentation of reason for early/late visit.

If a participant misses the visit window, every attempt should be made to contact participant and complete the SVR evaluation and other evaluations through the end of the study follow-up period.

At this visit, the following assessments will be done in all arms

- Scan biometric to confirm identity
- Administer a brief survey on substance use, risk behavior and quality of life
- Update medication history
- Provide updated contact/locator information
- EHR review, clinical exam, and vital signs
- Draw blood for HCV RNA testing
- Abstract HIV RNA information from government ART book (if HIV infected)
- Pregnancy test (if female)
- Schedule next appointment

The post-SVR evaluations will be scheduled in relation to when participants complete the SVR evaluations.

While COVID-19 safety precautions are in place, in order to reduce face-to-face contact, we will administer surveys, update medication history and collect locator information over the phone. Participants will have to come to the ICC for a brief exam and blood draw (and pregnancy test as needed). Exceptions will be made for this in-person requirement in cases where 1) COVID-19 precautions make travel to the site challenging; and 2) participants are in rehabilitation facilities or cannot travel to the site for another reason.

In cases where the HCV RNA ≥30 IU/ml and <1000 IU/ml, a repeat sample will be drawn ≥14 days after the initial sample as long as it is within the SVR window (i.e., up to 60 weeks after treatment completion)

12.2.5. Post-SVR evaluations

Post-SVR evaluations should be assessed on the majority of participants at the following time points: week 48, 72, 96, 120, 144, 168, 192, 216 For a minority who receive 24 weeks of treatment, these evaluations will take place at week 60, 84, 108, 132, 156, 180, 204, 228

The window for these visits is +/- 28 days. If this window is missed, the participant can complete the next scheduled visit.

Participants in all three arms who achieve SVR will visit the clinic every six months to assess HCV reinfection. In addition, all HIV/HCV co-infected participants will be followed every six months. The following assessments will be done:

- Scan biometric to confirm identity
- Administer a brief survey on substance use, risk behavior and quality of life
- Provide updated contact information
- Draw blood for HCV RNA (HCV CoreAg)
- Abstract HIV RNA information from government ART book (if HIV infected)
- Schedule next appointment

While COVID-19 safety precautions are in place, in order to reduce face-to-face contact, we will administer surveys, update medication history and collect locator information over the phone. Participants will have to come to the ICC for a blood draw.

12.2.6. Additional contact visits for Arm 3

Participants in Arm 3 will have additional contact visits where medication will be dispensed. This will range in frequency from 1-7 times per week depending on the frequency of observed doses. For participants receiving clinic-based DOT, the doses will be observed in the ICC and for participants receiving field-based DOT, the doses will be observed in the field.

At each contact, an outreach worker will record the participant's biometric to confirm identity, provide the medication dose, observe the dose being taken and plan the next contact.

12.2.7. Unplanned study evaluations

Unplanned visits can occur while participants are on treatment to address toxicities (Week 0 to 12 for most participants and Week 0 to Week 24 for those who receive 24 weeks of treatment). Participants will be provided with a telephone number that they can call if they are having problems (e.g., headache, fever, nausea etc.) while on study treatment. Participants will be connected to study staff (e.g., nurse/doctor as needed) to try and resolve problems over the phone.

If study staff feels that further investigation is needed to resolve the complaint, an unplanned study visit will be scheduled for any additional investigations that are needed. No specific laboratory testing is indicated for these visits but if safety laboratory tests are ordered they should be recorded in an eCRF.

If a participant provides information about study treatment disposition, use (or change in use) of reportable concomitant medications, or gives information about reportable adverse events (e.g., AEs leading to change in study treatment regardless of severity grade) at this unplanned study visit, then this information will be captured on the appropriate eCRFs.

Participants who become pregnant while on study medications or up to week 24 (or week 36 for those receiving 24 weeks of treatment) should contact the site to schedule an unplanned study visit.

12.2.8. Premature treatment discontinuation evaluations

Participants who plan to discontinue treatment or who have discontinued their study medication prior to completing the full 12-week (or 24-week) course will have been instructed to contact the site to alert them of premature discontinuation. These participants will be encouraged, like all other participants, to return for their SVR evaluation visit at week 24 and remain on the study through study completion. No adjustments to the timing of the SVR evaluation will be made for premature treatment discontinuation. Participants will be provided a number to call or send a text message informing the site of the stop date.

12.3 Instructions for Evaluations

12.3.1. Documentation of active HCV infection (HCV RNA+)

Those positive for HCV RNA ≥ 30 IU/ml prior to study entry will be considered to have active HCV infection.
Section 10.1.1 specifies assay requirements for HCV RNA testing
Results should be documented in the screening eCRF.

12.3.2. Documentation of HIV status and antiretroviral therapy regimen

Clients in the ICCs are offered HIV testing every 6 months. These HIV results are maintained in the EHR. In addition, all HIV positive participants who visit a government ART center receive an ART book which maintains a record of all laboratory testing that is done within government ART centers (i.e., CD4 cell count and HIV RNA) and all ART prescriptions and refills including the name of the medications, the number of pills dispensed and the dose. All of this information is abstracted monthly by ICC staff into the EHR. Using this EHR, HIV status, most recent CD4 cell count, HIV RNA level and ART refill will be documented in the screening eCRF. In cases where no HIV test has been done or the most recent HIV antibody test was negative and completed more than three months prior, an HIV antibody test will be required for screening purposes.

12.3.3. Calculated FIB-4 score

Calculated FIB-4 score is needed to determine cirrhosis status for all participants in order to determine treatment eligibility.

This calculation requires the following data: Participant age (years), serum alanine and aspartate aminotransferase level (U/L), and platelet count (10^9/L). All individuals will have received these tests as part of the background standard of care for ascertaining HCV treatment eligibility. The results will be abstracted from the EHR onto the Screening eCRF.

Please refer to http://gihep.com/calculators/hepatology/fibrosis-4-score/ to calculate the FIB-4 score.

FIB-4 will be documented in the screening eCRF

12.3.4. Documentation of cirrhosis status

Participants with calculated FIB-4 score of <3.25 are considered to be non-cirrhotic.

Participants with calculated FIB-4 score ≥3.25 are considered to have cirrhosis and must have a calculated CTP score of ≤6 (CTP A) to be considered a compensated cirrhotic.

Cirrhosis status will be documented in the screening eCRF.

12.3.5. Calculated Child-Turcotte Pugh (CTP) score

Calculated CTP score is needed only for participants who are considered cirrhotic as determined by the FIB-4 score (≥3.25). CTP score must be ≤6 corresponding to Class A to be included in the study.

This calculation requires the following data: total bilirubin (mg/dl), albumin (g/dl), International Normal Ratio (INR), clinical evaluation for ascites (absent, slight, or moderate), and clinical evaluation for hepatic encephalopathy as per West Haven criteria (none, mild to moderate [Grade1-2], severe [Grade 3-4]). All individuals will have received these tests/evaluations as part of the background standard of care for ascertaining HCV treatment eligibility. The results will be abstracted from the EHR onto the Screening eCRF.

Please refer to http://gihep.com/calculators/hepatology/child-pugh-score/ to calculate the CTP score.

12.3.6. Brief medical history

The medical history must include self-reported history of all signs and symptoms regardless of grade within 30 days prior to screening. In addition, information on the following diagnoses should be reported regardless of when the diagnosis was made:

- AIDS-defining conditions (only for HIV-1 co-infected participants)
- Bone fractures (verbal history accepted)
- Coronary heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis
- Chronic HCV (If available, appropriate documentation from medical records of chronic HCV-infection, defined as having a documented HCV-positive antibody serology for greater than 6 months)
- Chronic HBV

Any allergies to any medications and their formulations must also be documented.

12.3.7. Medication history

A complete medication history must be recorded, including start and stop dates.

Complete history
- Antiretroviral therapy
- Tuberculosis treatment
- Treatment for viral hepatitis (hepatitis B, hepatitis C)

Within 30 days of study entry
- Prescription drugs for treatment/prevention of opportunistic infections
- Other prescription drugs
- Non-prescription drugs (including homeopathic, ayurvedic, siddha)
- Acid suppressing medications such as proton pump inhibitors (PPIs)

12.3.8. Clinical evaluations

12.3.8.1. Complete physical exam. A complete physical examination will be performed as part of the background assessment of HCV treatment eligibility. At a minimum, this should include an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac exam; abdominal exam; and examination of the lower extremities for edema. The complete physical exam will also include signs and symptoms, diagnoses, and vital signs (height, weight, temperature, pulse, respiration rate, and blood pressure).

Post entry, the following targeted events will be recorded regardless of grade.
- Uterine pregnancy
- AIDS-defining conditions (refer to the CDC HIV Classification and the WHO Staging System for HIV Infection and Disease)
- Tuberculosis
- Chronic Hepatitis B virus (HBV)
- Ascites
- Hepatic Encephalopathy

Refer to **Section 13.2.3** for AE collection requirements.

12.3.8.2. Height. Height (in cm) will be collected once at study screening.

12.3.8.3. Weight. Weight (in kg) will be collected at study screening and the SVR evaluation visit.

12.3.8.4. Symptom screen for tuberculosis. At screening, a standard 4-symptom screening tool will be used for tuberculosis. Those who screen positive will be asked to provide a sputum sample which will be evaluated by the nearest Revised National Tuberculosis Program (RNTCP) center. Those whose sputum test negative will be eligible to enroll. Those who test positive will be referred to complete TB treatment prior to enrolling in the trial.

12.3.8.5. Concomitant medications. At entry, on treatment, and at the SVR evaluation visits, new and discontinued concomitant medications will be recorded on the eCRFs. See **Section 11.2.4** for concomitant medications.

12.3.8.6. Study treatment (intervention) modifications. Treatment completion and any modifications during therapy will be recorded in the eCRF.

Treatment interruptions > 7 days and/or permanent treatment discontinuation should also be reported (See **Section 14.1.2**.).

12.3.9. Laboratory evaluations

Laboratory testing conducted as part of the standard of care at the ICCs will determine eligibility for HCV treatment.

Among those enrolled in the trial, minimal laboratory monitoring will be used while participants are on treatment. The majority will only receive laboratory testing to determine treatment eligibility and at the SVR evaluation visit.

HCV genotype testing will only be done for HIV/HCV coinfected clients on EFV-based ART who have evidence of cirrhosis in order to guide duration in case the patient is unable to switch from EFV to another allowable ART regimen for co-administration with SOF/VEL.

In all others, no safety labs will be recommended on treatment unless clinically indicated.

Laboratory testing at the SVR evaluation visit will determine the primary study outcome. Laboratory testing at post-treatment follow-up visits will determine secondary outcomes (reinfection). Laboratory testing will be conducted 1) on-site; 2) using local laboratories; and 3) at the central YRGCARE laboratory in Chennai, India.

A list of laboratories for each city can be found in the Study **Manual of Operations**. Laboratory testing to determine HCV treatment eligibility will be recorded in the EHR and abstracted into an eCRF. All on-treatment and post-treatment laboratory results will be recorded in an eCRF.

12.3.9.1. Complete blood count. Hemoglobin (Hb), hematocrit, red blood cell (RBC) count, white blood cell (WBC) count, platelet count.

12.3.9.2. Liver function tests. AST, ALT, ALP, GGT, total protein, albumin, bilirubin –direct, indirect and total.

12.3.9.3. Renal function tests. Serum creatinine, sodium, blood urea nitrogen.

12.3.9.4. Creatinine Clearance (CrCl). CrCl will be calculated throughout the study using Cockcroft-Gault method. Refer to the Cockcroft-Gault calculator https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation

12.3.9.5. International Normalized Ratio (INR). This will be calculated for cirrhosis determination

12.3.9.6. Pregnancy test (women). For women with reproductive potential: Serum or urine β-

human chorionic gonadotropic. (Urine test must have a sensitivity of <25 mIU/mL.) Record pregnancy and pregnancy outcome.

12.3.9.7. HBsAg. HBsAg will be performed at an approved local laboratory.

Chronic HBV infection is defined by the presence of hepatitis B surface antigen in serum (HBsAg+) at screening.

12.3.9.8. Immunologic studies.

CD4
If a CD4 within 90 days prior to screening is not available in the EHR, a CD4 count will be obtained from an approved local laboratory (HIV-positive participants).

12.3.9.9. Virologic studies.

HCV RNA testing
Screening HCV RNA and SVR HCV RNA testing will be conducted at the YRGCARE Infectious Disease Laboratory in Chennai, India, which is a DAIDS-certified laboratory.

Samples for HCV RNA testing will be processed and shipped as described in **Section 12.3.9.11**.

Any sample with HCV RNA between 30 – 1000 IU/ml will require resampling for confirmation in a second sample drawn ≥14 days after the initial sample.

HIV RNA testing
HIV RNA testing is generally done at government ART centers. Available HIV RNA results will be abstracted from the ICC EHR.

HCV Core Antigen testing.
For post-SVR visits, re-infection will be assessed using the Abbott ARCHITECT HCV Ag assay. This testing will be conducted at the YRGCARE Infectious Disease Laboratory in Chennai, India.

Samples for HCV Core Antigen testing will be processed and shipped as described in **Section 12.3.9.11**.

12.3.9.10. Stored plasma/serum. Stored plasma and serum will be collected at the indicated visits for future HCV/HIV studies and shipped to the central YRGCARE Infectious Disease Laboratory.

Stored specimens may be used for HCV genotyping/sequencing needed to differentiate between relapse and reinfection among participants failing to achieve SVR. We will also test for the presence of resistance-associated substitutions (RASs) in these specimens by sequencing the nonstructural protein 5A (NS5A) and nonstructural protein 5B (NS5B) regions.

12.3.9.11. Specimen preparation, handling and shipping. All staff handling laboratory specimens will undergo training in Good Clinical Laboratory Practices (GCLP). Additional training certification and recertification will be provided by the Central YRGCARE team in India. The YRGCARE lab is a DAIDS certified laboratory. Certification of the personnel and the procedures on specimen collection, preparation, handling, storage and shipping will be required before sites start collecting and shipping specimens.

Specimens will be stored on-site in a refrigerator for up to 4 days prior to shipping to the YRGCARE Infectious Diseases Laboratory. Each site will be equipped with a printer to print electronically generated barcoded labels with the participant's study ID and date of collection. Specimens should be shipped once weekly to the central YRGCARE Infectious Diseases Laboratory at: Voluntary Health Services Campus
Taramani, Chennai 600 113
Contact: P Balakrishnan

Specimens will be shipped via courier using appropriate biohazard precautions. All shipments should include a specimen-tracking log and once they arrive at the YRGCARE Infectious Disease Laboratory will be logged into the Laboratory Data Management System. Specimens of serum and plasma will be aliquoted into smaller tubes for storage and stored at -70 degrees Celsius for 5 years after the study is completed.

12.3.9.12. Biohazard containment. Transmission of HIV and other blood borne pathogens can occur through contact with contaminated needles, blood, and blood products. Respiratory pathogens such Mycobacterium tuberculosis (MTB) are transmitted by inhalation of droplet nuclei. Appropriate blood, secretion, and respiratory precautions will be employed by all personnel in the collection of clinical samples and the shipping and handling of all clinical samples and isolates for this study, as currently recommended by the WHO and the National Institutes of Health.

All protocol specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650. Culture isolates, if obtained in this study, are to be shipped as specified for UN 2814 Category A Infectious Substances.

12.3.10. Questionnaires

Screening questionnaire**.** This will be a brief questionnaire to capture other screening criteria including intention to migrate, psychological fitness, pregnancy intentions, etc.

Responses should be recorded in a screening eCRF. This is a one-time questionnaire.

Demographics questionnaire
This questionnaire will be adapted from questionnaires previously used in this population to capture age, sex, marital status, education, income and housing status.

Responses should be recorded in an eCRF. This questionnaire will be administered at the Entry visit, SVR evaluation visit, and post-SVR visits.

Social/family support
We will use the Medical Outcomes Study Social Support Survey[93] which captures information on functional support in five dimensions (emotional, informational, tangible, positive social interaction and affectionate). Additional questions will be asked about disclosure of HCV/HIV and substance use to family members/friends.

Responses should be recorded in an eCRF. This is a one-time questionnaire that will be administered at the Entry visit.

Quality of life
The EQ-5D is a validated instrument used to collect data about quality of life (http://www.euroqol.org). The instrument asks questions and each has three possible responses (EQ5D-3L version). The instrument asks respondents to comment on their degree of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and then ask participants to record their current health-related quality of life state using a vertical visual analogue scale (0-100 range). The instrument has been translated into a variety of languages including Hindi and Punjabi and is available as a paper form, a computer-based form, a tablet/cell phone form, or as an interview.

Responses should be recorded in an eCRF. This questionnaire will be administered at the Entry visit, SVR evaluation visit, and post-SVR visits.

Substance Use and Risk Behavior Questionnaire
We will use a questionnaire that has been adapted from a variety of sources (WHO ASSIST,[94] PhenX toolkit, AUDIT and existing survey) for use in India. This survey includes information on the type, route and frequency of drug and alcohol use. In addition, this survey will collect information on risk factors for nonadherence and for reinfection including data on the types and numbers of sharing/network partners, locations of drug injection, use of shooting galleries and incarceration.

This questionnaire will also include information on sexual risk behavior including overlap between sexual and drug network members, unprotected sex acts and history/symptoms of sexually transmitted infections.

Responses should be recorded in an eCRF. This questionnaire will be administered at all study visits (Entry, on-treatment visits, SVR evaluation visit and post-SVR visits).

Adherence Assessment
Adherence will be captured at the on treatment visits (4, 8 and 12 weeks and additionally at 18 and 24 weeks for those receiving 24 weeks of treatment). Participants will be asked to estimate their adherence over the past 30 days using the Visual Analogue Scale which asks participants to estimate the percentage of doses taken (from 0 to 100%). At each of these visits, participants will also be asked about barriers to adherence. Finally, participants will be asked to bring in medication bottles at the on-treatment visits and remaining doses will be counted.

Depressive symptoms
Depressive symptoms will be captured using the PHQ-9. This will be collected at the entry visit and the SVR 12 visit.

HCV treatment readiness
A standardized questionnaire on readiness for HCV treatment will be administered at the entry visit.

COVID symptoms/testing history
At every visit, a questionnaire will be administered to screen for recent COVID-19 symptoms, testing and treatment history.

12.3.11. Biometric

A biometric system will be used to track participants across all study visits. The process involves scanning participants' iris/fingerprint/face and converting these scans to unique alphanumeric

codes using proprietary software. Images are not saved and alphanumeric codes cannot be converted back to images. These alphanumeric codes will become the unique identifier for each study participant, such that each time the client visits the ICC, an iris/fingerprint/face scan is all that is needed to identify him/her.

12.3.12. Locator information

At the screening visit, all participants will be asked to provide their primary mode of contact (e.g., telephone, email, text, or social media) and their secondary mode of contact. The site will capture these options for mode of contact and will also capture information on hang out locations. Sites will also capture information on another person that the site can contact if the participant cannot be reached (e.g., spouse, friend, neighbor, etc.) as well as their contact information. If there are changes to participants' contact and locator information, updates will be recorded at each visit.

12.3.13. Counseling

Adherence counseling

Adherence education and counseling will be conducted for all participants at study entry and at all on treatment visits.

Adherence education and counseling will be recorded on the eCRF.

Cirrhosis/liver health counseling

All compensated cirrhotics will be counseled on secondary prevention and long-term surveillance of liver disease at study entry, end of treatment visit (week 12 or 24) and all following visits.

Cirrhosis counseling will be recorded on the eCRF.

HCV risk reduction counseling

HCV risk-reduction counseling will be administered to all participants at study entry and all following visits.

HCV risk reduction counseling will be recorded on the eCRF.

12.3.14. Medication dose observed

For all arms, study staff will observe the first dose taken by the participant before he/she leaves the site and record this observation on an eCRF.

Additional doses will be observed for Arm 3 participants.

13. ASSESMENT OF SAFETY

13.1 Safety Assessment Overview

This section provides information on the definition of adverse events (AE), serious adverse events (SAE) and the procedures for reporting. Procedures for prompt reporting of AE and SAE will be standardized across the field sites.

13.2 Adverse Event Procedures and Reporting Requirements

13.2.1. Definition of Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

13.2.2. Grading severity of events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017, must be used and is available on the DAIDS Regulatory Support Center (RSC) Web site at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables .

13.2.3. Adverse Event collection requirements for this protocol

This trial will be evaluating the effectiveness of behavioral interventions. All medications that will be used are approved by the US FDA and the Drug Controller General India.

All AEs that occur after the entry visit and up to the SVR evaluation visit must be recorded on the eCRFs if any of the following criteria have been met.

- All grade ≥ 3 AEs
- All AEs that led to a change in treatment/intervention regardless of grade
- All AEs meeting SAE definition or expedited adverse event (EAE) reporting requirement

All AEs that are reported will have their severity graded. Severity will be graded as per Division of AIDS guidelines: http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables.http://rsc.tech-res.com/safetyandpharmacovigilance/.

Serious Adverse Events (SAEs). Serious adverse events will be reported to the YRGCARE and JHMI IRB within 7 days of when the site staff are notified.

An SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above).

14. CLINICAL MANAGEMENT

14.1 Clinical Management of Adverse Events

14.1.2. Drug toxicity

Criteria for participant management, dose interruptions, dose adjustments and discontinuation, or changes in treatment will be described only for toxicities attributable to study drugs (either SOF/VEL or SOF/DAC). The grading system for drug toxicities is located in the DAIDS AE Grading Table (see **Section 13.2.2**).

NOTE: The PIs must be notified via e-mail within 7 days regarding toxicities that result in a change in study regimen

It is possible that some participants will experience transient or prolonged AEs during the study. In this trial, the scheduled on-treatment visits are as per the standard of care of treatment delivery in India. In addition, participants can come into the study site at any time to one of the study clinicians in order for AEs to be identified. Detailed data on AEs that are reported at study visits and in-between study visits will be collected in the eCRFs.

14.1.3. Management of side effects of SOF/VEL and SOF/DAC

There are no signature abnormalities associated with SOF/VEL or SOF/DAC. If an SAE occurs, the site clinician should contact one of the two protocol physicians and has the option to discontinue study treatment. However, prior to the discontinuation of study drugs, the study PIs should be notified by email within 7 days of its occurrence.

Participants who meet any of the following laboratory criteria should stop treatment with SOF/VEL or SOF/DAC:

- Confirmed elevation of ALT and/or AST >5 x entry values measured while on study treatment measured at planned or unplanned study visits.
- Confirmed direct bilirubin 3 x ULN and >2.0 mg/dL
- Any Grade 3 or greater rash associated with constitutional symptoms assessed as related to treatment with SOF/VEL or SOF/DAC.
- Any Grade 4 event assessed as related to treatment with SOF/VEL or SOF/DAC.

Dose modification of SOF/VEL and SOF/DAC will not be allowed in the study. If SOF/VEL or SOF/DAC is discontinued for toxicity reasons, it should not be restarted.

NOTE: Grades 1 and 2 AEs associated with SOF/VEL and SOF/DAC require no change in study treatment.

14.2 Pregnancy

Because there is insufficient data on the safety of SOF/VEL and SOF/DAC during pregnancy, pregnancy will result in the discontinuation of study medication and initiation of counseling regarding the lack of information on safety of SOF/VEL or SOF/DAC in pregnancy. While there was a recent demonstration of the safety of SOF/ledipasvir among pregnant women enrolled at 23-24 weeks of gestation,[95] the women enrolled in this study will be receiving different regimens. Moreover, if women become pregnant during the course of this study, it is likely that their HCV treatment exposure would be within the first trimester of their pregnancy and the safety of the medications during that time period has not yet been established.

Participants in whom pregnancy is suspected should receive a pregnancy test during a study visit. Additionally, participants who suspect pregnancy or become pregnant should contact the site to schedule an unplanned study visit (only up to week 24) and will be followed on study/off-treatment until study completion. A visit following the end of pregnancy will be conducted for evidence of AEs in the participant, and an outcome eCRF will be completed. Male participants whose partners become pregnant will continue treatment.

If a female participant has completed the study or chooses to discontinue from the study before the end of the pregnancy, site staff will request permission to contact her regarding pregnancy outcomes at the end of pregnancy. If the information is obtained, pregnancy outcomes will be submitted on an eCRF at the end of the pregnancy.

Pregnancy and pregnancy outcome will be recorded on the eCRFs. Pregnancy outcomes will also be reported to the Drug Controller General India.

14.3 Treatment Failure

Participants in the trial who fail treatment will be referred to the nearest government hospital/program for possible retreatment. Retreatment will not be offered through the ICC.

14.4 Criteria for Discontinuation

14.4.1. Permanent and premature treatment discontinuation

Potential reasons for permanent or premature discontinuation of study treatment (SOF/VEL or SOF/DAC) are:

- Drug-related toxicity (see **Section 14.1.2**).
- Requirement for prohibited concomitant medications (see **Section 11.2.4**).
- Pregnancy in a female participant.
- Breastfeeding.
- Completion of treatment as defined in the protocol.
- Participant request to discontinue treatment for any reason.
- Clinical reasons believed life threatening by the physician, even if not addressed in the drug toxicity section of the protocol.

NOTE: It is important to determine whether the treatment discontinuation is primarily due to an AE, lack of efficacy, or other reason and record this in the eCRF.

14.4.2. Premature study discontinuation

Potential reasons for permanent or premature discontinuation of study participation are:

- Request by the participant to withdraw.
- Request of a study clinician if s/he thinks the study is no longer in the best interest of the participant.
- At the discretion of the IRB/Ethics Committee, National Institute of Allergy and Infectious Disease (NIAID), Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator.

The reason for premature study discontinuation will be recorded in an eCRF.

15. STATISTICAL CONSIDERATIONS

15.1 Overview and General Design Issues

The primary objective of the protocol is to evaluate whether HCV treatment outcomes (sustained virologic response) in HCV mono- and HIV/HCV co-infected PWID can be optimized by tailoring treatment support in 7 PWID-focused integrated HIV/HCV prevention/treatment centers. This is an unblinded individually randomized trial with an unbalanced allocation approach. An algorithm (based on early ART refills/HIV viral suppression) will be used to triage clients into two strata: minimal and elevated risk for failure. Using an unbalanced randomization approach, the goal is to assess the efficacy of low, medium and high intensity treatment support strategies within the two strata of risk (minimal and elevated) and overall sample. Eligible study participants include PWID clients who are eligible for HCV treatment in one of 7 integrated HIV/harm reduction centers across India. Study staff and participants will be blinded to whether participants were designated as minimal or elevated risk according to the prediction algorithm.

The primary outcome of this trial is SVR which will be assessed 10 – 60 weeks after treatment completion. All participants who achieve the primary outcome and those HIV co-infected will be followed for up to an additional 2.5 years to measure secondary outcomes of HCV reinfection and HIV viral suppression. The results from this trial will be used to guide programs in optimizing HCV treatment outcomes among PWID.

15.2 Study Endpoints

15.2.1. Primary endpoint(s)

Sustained virologic response (SVR) defined as HCV RNA < lower limit of quantification (LLOQ) 10 – 60 weeks after completion of treatment (cure).

15.2.2. Secondary endpoint(s)

1. Treatment completion defined as completing the prescribed course of treatment (12/24 weeks)

2. Treatment adherence to study treatment as self-reported by study participants

3. HCV reinfection defined as testing positive for HCV Core Ag after achieving SVR

4. HIV viral suppression among HIV/HCV coinfected participants defined as HIV RNA less than LLOQ (HIV RNA <150 copies/ml)

15.3 Study Objectives and Hypothesis/Hypotheses

15.3.1. Primary objective / hypotheses

Primary objective: To evaluate whether the intensity of treatment adherence support affects sustained virologic response rates in HCV mono- and HIV/HCV co-infected participants receiving DAAs in PWID-focused centers

Hypotheses:

1. Among PWID at elevated risk for treatment failure, PWID receiving the high intensity intervention will have significantly higher SVR than those receiving either the medium or the low intensity interventions.

   1a. Among PWID at minimal risk for treatment failure, PWID receiving either the high or the medium intensity intervention will have significantly higher SVR than those receiving the low intensity interventions.

The formal null hypothesis is no difference in SVR and the alternate is a difference in SVR. The trial is designed for superiority assessment; however, if there is failure to detect a statistically significant difference between support strategies across any particular stratum, a lesser objective of interest is non-inferiority with a pre-specified non-inferiority margin.

15.3.2. Secondary objectives / hypotheses

15.3.2.1. To evaluate whether the intensity of treatment adherence support affects HCV treatment completion rates.

Hypothesis: Among PWID at elevated risk for treatment failure, PWID receiving the high intensity intervention will have significantly higher treatment completion than those receiving either the medium or the low intensity interventions.

Hypothesis: Among PWID at minimal risk for treatment failure, PWID receiving either the high or the medium intensity intervention will have significantly higher treatment completion than those receiving the low intensity interventions.

15.3.2.2. To evaluate whether the intensity of treatment adherence support affects HCV treatment adherence.

Hypothesis: Among PWID at elevated risk for treatment failure, PWID receiving the high intensity intervention will have significantly higher adherence than those receiving either the medium or the low intensity interventions.

Hypothesis: Among PWID at minimal risk of treatment failure, PWID receiving either the high or the medium intensity intervention will have significantly higher adherence than those receiving the low intensity intervention.

15.3.2.3. To estimate the incidence and correlates of HCV reinfection among HCV mono- and HIV/HCV coinfected PWID who achieve HCV cure.

Hypothesis: HCV reinfection will be lower among clients who have higher attendance at OAT programs.

15.3.2.4. To evaluate the impact of HCV cure on HIV viral suppression among HIV/HCV coinfected PWID.

Hypothesis: Among HIV/HCV co-infected PWID, HIV viral suppression will be higher after achievement of HCV cure.

15.4 Sample Size Considerations

The anticipated sample size for this trial is 3,000 with approximately 420 recruited at each site over an 18-24 month period. Approximately 15-20 persons per month per site will be recruited. Recruitment may be unbalanced across the sites due to larger client volume at some sites. Sample size calculations were based on the primary outcome: sustained virologic response (SVR) defined as HCV RNA < lower limit of quantification (LLOQ) 10 to 60 weeks after completion of treatment (cure) and an intention to treat analysis. The trial is defined for superiority assessment; however, if no statistically significant difference between support strategies is detected within a specific stratum, a lesser objective of interest is non-inferiority with a pre-specified non-inferiority margin.

ELEVATED RISK STRATUM	**N=1500 total (750 high intensity, 500 medium intensity, 250 low intensity)**		**N=1225 total (615 high intensity, 410 medium intensity, 200 low intensity)**		**N=1000 total (500 high intensity, 333 medium intensity, 167 low intensity)**	
SVR in PWID receiving low/medium intensity intervention	RR comparing high to low intensity	RR comparing high to medium intensity	RR comparing high to low intensity	RR comparing high to medium intensity	RR comparing high to low intensity	RR comparing high to medium intensity
0.80	1.09	1.08	1.10	1.08	1.11	1.09
0.85	1.08	1.06	1.08	1.07	1.09	1.08
0.90	1.06	1.05	1.06	1.05	1.07	1.06
0.95	1.04	1.03	1.04	1.03	1.04	1.04
MINIMAL RISK STRATUM	**N=1500 total (750 low intensity, 500 medium intensity, 250 high intensity)**		**N=1225 total (615 low intensity, 410 medium intensity, 200 high intensity)**		**N=1000 total (500 low intensity, 333 medium intensity, 167 high intensity)**	
SVR in PWID receiving low intensity intervention	RR comparing high to low intensity	RR comparing medium to low intensity	RR comparing high to low intensity	RR comparing medium to low intensity	RR comparing high to low intensity	RR comparing medium to low intensity
0.80	1.10	1.08	1.11	1.08	1.12	1.09
0.85	1.08	1.06	1.09	1.07	1.09	1.08
0.90	1.06	1.05	1.07	1.05	1.07	1.06
0.95	1.04	1.03	1.04	1.03	1.05	1.04

Table 15.4.1. Relative risk (RR) of sustained virologic response (SVR) across stratum of risk for treatment failure (elevated and minimal risk).

Based on preliminary data, minimal and elevated risk strata will be defined by the median of the prognostic score (estimated 1500 per stratum). However, the exact distribution will be based on the cutoff that maximizes predictive accuracy according to AUROC analysis. As such, an estimated 1000-1500 persons will be within the stratum that has the lower number of participants. **Table 15.4.1** illustrates the minimal detectable relative risks (RR) that can be detected for a range of scenarios assuming a two-sided alpha=0.05 and 80% power. The scenarios illustrate detectable effect sizes with the optimal sample size (n=3000) but also with a reduced total sample size of 2450 (assuming 1000-1225 will still be allocated per stratum).

For example, in the elevated risk stratum, assuming an SVR of 85% in those receiving the low/medium intensity intervention, a RR of 1.06 comparing SVR in those receiving the high intensity intervention to those receiving the medium intensity intervention and 1.08 comparing those receiving the high intensity intervention to those receiving the low intensity intervention can be detected if the total allocated to this stratum is 1500. Power will be slightly reduced if the total sample size in this stratum is 1000. Similarly, in the minimal risk stratum, if a 95% SVR rate is observed in those receiving the low intensity intervention, a RR of 1.03 comparing the medium intensity to the low intensity intervention and a RR of 1.04 comparing the high intensity intervention to the low intensity intervention can be detected with a sample size of 1500 per stratum. Power will be increased if a lower SVR (<95%) is observed in the comparator group.

If no difference is detected in a comparison of two arms, non-inferiority will be established if SVR in those receiving one intensity of intervention compared to another is less than 3.4% (non-inferiority with sample size of 1500 and SVR=95% in the comparison group). The margin is 4.5% if the sample size is 1000 in one of the groups. Non-inferiority margins <5% are clinically meaningful. Power for secondary outcomes of treatment completion is comparable.

15.5 Enrollment/Stratification/Randomization/Blinding Procedures

This study uses a "precision" clinical trial framework that leverages prior information to target treatment adherence support to individuals based upon their characteristics (i.e., propensity for nonadherence) while preserving ability to assess the average treatment effect and differences by arms within groups defined by these characteristics (**Figure 15.5**). Specifically, an individual, unblinded, unbalanced, blocked allocation approach based on prior information of the patient's propensity for failure will be used.

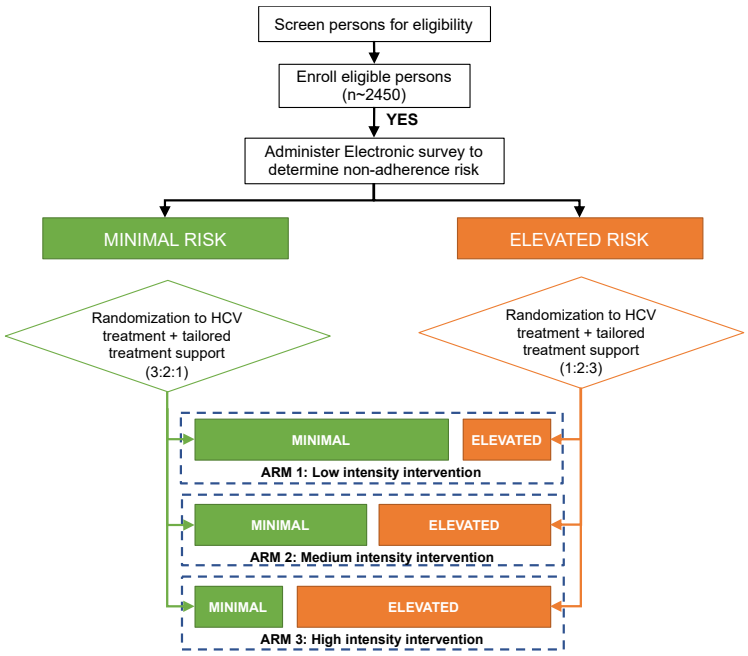


Figure 15.5. Precision randomization strategy

Data on early ART refills/HIV viral suppression (3-6 months after ART initiation) from existing ICCs will be used to develop an algorithm to predict propensity for HCV treatment failure. We are currently unaware of any large databases that contain information on SVR among active PWID in India that we could use and therefore, opted to use early ART refills/viral suppression among HIV-positive persons as a surrogate. The time frame being used is comparable to a full course of HCV treatment. We will develop the score using an approach that incorporates an internal-external cross validation procedure[96] where the unit for splitting data will be study site. Each site will be left out once with validation conducted on the remaining pooled set of data. The final model is based on the pooled dataset which can be considered to be an externally validated model. This assures that the final model is based on the pooled data thus maximizing sample size while at the same time tempering overoptimistic model performance in an independent set of data.

In a preliminary analysis, among 119 clients newly initiating ART, we developed a model that had high predictive accuracy (area under the receiver operating characteristics curve=0.81) for early adherence. Importantly all of the factors included in this model (age, employment, injection frequency, OAT use, living with spouse/family, having told someone about their HIV status and readiness for treatment) are either routinely captured in the ICC or can be added to a brief intake survey. We will modify this algorithm based on an expanded analysis that includes ~500 persons initiating ART. We anticipate splitting at the median of the score but this will be reassessed once the model is complete. Distributions of the score within independent samples of the population will be assessed prior to implementation.

At the Entry visit, prior to randomization and treatment initiation, each participant will undergo a short survey to capture information on barriers/facilitators to treatment adherence identified in the prediction model. Responses to this survey will be captured in an eCRF and integrated with other data from the EHR. The algorithm will be used to classify persons into two strata according to their propensity for HCV treatment failure (minimal or elevated risk).

Individuals will be preferentially randomized to the support level that matches their failure risk. Those at elevated risk for treatment failure will be randomized at an allocation ratio of 3:2:1 for high, medium and low intensity support respectively. Those at minimal risk will be randomized at a ratio of 1:2:3 to high, medium and low-intensity support, respectively.

Randomization will be integrated into the EHR. The Study Nurse who will complete the survey will receive the determination of study arm from an automated program. Both study staff and study participants will be blinded to the designation of minimal/elevated risk stratum.

15.6 Participant Enrollment and Follow-up

We anticipate enrolling 3,000 (approximately 420 per site) persons over a period of 18-24 months with an average of 15-20 participants per site per month. After enrollment, participants will be followed while they are on treatment (for 12 or 24 weeks) through to an SVR evaluation visit 10 – 60 weeks after treatment completion. This will be the minimum amount of follow-up for all those enrolled. Following this, those who achieve SVR and those who are HIV/HCV co-infected (regardless of SVR) will have semi-annual visits thereafter to monitor reinfection. Follow-up will be complete at the SVR evaluation visit for those who do not achieve SVR and are not HIV/HCV coinfected. The maximum follow-up post the SVR evaluation visit for those who achieve SVR is 30 months for a total follow-up of 36 months. The goal will be that everyone who achieves SVR has at least one semi-annual visit after the SVR evaluation visit but it is possible that some individuals who are enrolled late do not have any post SVR follow-up.

15.7 Data and Safety Monitoring

Data from the trial will be reviewed monthly with more formal Data, Safety, and Monitoring (DSM) reports occurring approximately semi-annually from first participants' first visit date. In addition, a Data and Safety Monitoring Board (DSMB) will be formed that includes four to five members with relevant expertise (e.g., PWID, HCV treatment, treatment interventions, biostatistics/clinical trial design and monitoring) but who are independent from the study investigators with no conflicts of interest. See details in the **Data and Safety Monitoring Plan**.

15.7.1. Planned interim analyses and stopping guidelines

No interim analysis will be conducted as power to detect differences will be limited for the stratum specific analyses which represent the primary outcome.

15.7.2. Analysis plan

A brief description of primary and secondary outcome analyses is provided below. Additional details particularly on sensitivity analyses, exploratory analyses and subgroup analyses can be found in the Statistical Analyses Plan

15.7.2.1. Primary outcome.

The primary individual-level outcome is sustained virologic response (SVR) defined as HCV RNA < lower limit of quantification (LLOQ) 10 – 60 weeks after completion of treatment (cure). The primary analysis will be intention to treat and will be stratified by the risk of treatment failure (minimal and elevated).

The primary analysis will compare the proportion achieving SVR across level of support (low, medium, high intensity) within the two strata of risk (minimal and elevated) independently. Using a log-binomial or poisson regression model (due to the high prevalence of the outcome) with adjustment for site, in the elevated risk stratum, the proportion achieving SVR in those who received the low or moderate intensity interventions will be compared to those who received the high intensity intervention (in separate models) resulting in a relative risk (RR).

Primary comparisons will be intention to treat. That is the study population for this analysis will include everyone who was randomized. Individuals with missing data on the outcome of interest either due to loss-to-follow-up or death will be treated as failures. For those at minimal risk of failure, analyses will be similar.

Per protocol analysis. We will conduct a per protocol analysis which will exclude individuals which will exclude individuals who died prior to SVR assessment, who are alive but lost to follow-up (i.e., do not complete the SVR visit) and those who prematurely discontinued treatment. The study population for this analysis will include everyone who was randomized, completed a treatment course and completed the SVR evaluation visit.

Sensitivity Analyses. The Statistical Analysis protocol describes several sensitivity analyses to account for study site differently and to account for covariates that are differentially distributed by arm or are prognostic for the outcome. Additionally, we will conduct additional analyses of the primary outcome to account for missing data/nonadherence related to the primary outcome. Of interest is estimating the most beneficial effect of the higher intensity intervention as if everyone fully complied and there were no losses to follow-up or nonadherence to the intervention. Therefore, missing data will result from persons who do not complete the SVR visit within the window including both those who are lost to follow-up before and after treatment completion. We will conduct an additional per protocol analysis which will exclude individuals who are alive but lost to follow-up (i.e., do not complete the SVR visit) but account for the informative lost to follow-up using inverse probability censoring weights. Further, we will include the randomization to the different intervention arms as an instrumental variable. An instrumental variable analysis estimates the “complier” average treatment effect. Therefore, by using the randomization as an instrumental variable for the treatment arms, we would be able to estimate the complier treatment effect for those that fully comply with the intervention. A second approach will use fully specified conditional specification multiple imputation of the SVR outcome based on only two variables: treatment completion and adherence. In this analysis, undetermined SVR due to death will not be imputed; deaths will be treated as SVR failures. Additionally, assessing the relationship of the treatment arms with lost to follow-up is of interest in and of itself. This is because as an implementation strategy, policy makers would need to know the potential for loss to a program that they are implementing. Therefore, a time to lost to follow-up analysis will be examined using standard survival methods and accounting for prognostic score.

Non-inferiority analyses. Additionally, while the overall trial is designed to assess superiority, if there is a failure to identify that one support intervention is superior to another, sensitivity analyses will examine non-inferiority particularly within the minimal risk stratum using a pre-specified non-inferiority margin (i.e., that among those at minimal risk for treatment failure, the low intensity intervention is non-inferior to the medium and high-intensity interventions).

Subgroup and Exploratory Analyses. These are described in the Statistical Analysis Plan.

15.7.2.2. Secondary outcomes.

Secondary outcomes are 1) treatment completion defined as completing the prescribed course of treatment (12/24 weeks); 2) self-reported adherence; 3) reinfection defined as testing positive for HCV Core Ag after achieving SVR; and 4) HIV viral suppression defined as HIV RNA<LLOQl.

Treatment completion (secondary outcome). Those who prematurely discontinue treatment or are lost-to-follow-up prior to the completion of this visit will be considered as failures for this analysis. Using a log-binomial or poisson regression model (due to the high prevalence of the outcome), with adjustment for site, in the elevated risk stratum, the proportion completing treatment in those who received the low or moderate intensity interventions will be compared to those who received the high intensity intervention (in separate models) resulting in a relative risk (RR). For those at minimal risk of failure, analyses will be similar.

Sensitivity analyses. Sensitivity analyses similar to the primary outcome are described in the Statistical Analysis Plan.

Non-inferiority analyses. As with the primary outcome, if there is a failure to identify that one support intervention is superior to another, sensitivity analyses will examine non-inferiority particularly within the minimal risk stratum using a pre-specified non-inferiority margin (i.e., that among those at minimal risk for treatment failure, the low intensity intervention is non-inferior to the medium and high-intensity interventions).

Subgroup analyses. These are described in the Statistical Analysis Plan.

Adherence (secondary outcome). Adherence will be defined both using both self-reported data and objective data on refills completed and pill counts. It will be analyzed as both a continuous outcome (e.g., percentage of doses reported as taken; percentage of doses taken according to refills completed/pill counts) and a dichotomous variable (e.g., >90% of doses reported as taken; >90% of doses taken according to refills completed/pill counts). We will use both self-reported adherence as well as For the dichotomous adherence outcome, analyses will be conducted as they are specified for the primary outcome. For the continuous variable, the analysis will compare the percentage value of adherence across level of support (low, medium, high intensity) within the two strata of risk. Using a linear regression model, in the elevated risk stratum, the difference in adherence level for those who received the low and moderate intensity interventions will be compared to those who received the high intensity intervention. In this analysis, adherence will be calculated based on the data from the surveys at 4, 8 and 12 weeks. The comparisons will be adjusted only for site. For those at minimal risk of failure, analyses will be similar.

Per protocol analysis. We will conduct a per protocol analysis which will exclude individuals who died or were lost to follow-up before the end of treatment or who discontinued treatment prematurely.

Sensitivity Analyses. We will conduct sensitivity analyses as outlined in the Statistical Analysis plan similar to those described for the primary outcome include those to account for missing data due to missed visits. Specifically, we will use fully specified conditional specification multiple imputation of the SVR outcome based on available adherence reports.

Reinfection (secondary outcome). Reinfection will be defined as testing positive for HCV Core Ag after achieving SVR. This may be at any of the post SVR follow-up visits. To evaluate factors independently associated with reinfection, all clients who achieve SVR and have at least one subsequent HCV Core Ag assessment will be included. Using survival analysis, factors associated with reinfection will be assessed. These including ongoing substance use, needle sharing, OAT, SSP use, HIV status and frequency of visits to the ICC. We will also evaluate whether the risk stratum or intervention had impact on reinfection outcomes as well as the re-infection rate over time elapsed since treatment completion. In order to account for missing data due to loss-to-follow-up, we will use inverse-weighting methods.[97,98]

HIV viral suppression (secondary outcome). Annual assessments of HIV viral load among HIV/HCV coinfected participants in the 7 ICCs are expected as part of other ICC activities and standard of care at Indian government ART centers. All available viral load measurements for HIV/HCV co-infected PWID enrolled in the trial will be used. Viral suppression will be defined as HIV RNA <LLOQ. We will compare viral suppression across two groups defined by primary outcome status, which will be cured vs. not cured using logistic regression with generalized estimating equations (GEE) to account for repeated measures within individuals. All potentially confounding factors known to be associated with HCV cure and HIV viral suppression in this population including demographics, substance use, needle sharing, OAT, SSP use, social support and frequency of visits to the ICC will be accounted for. Analyses will be combined across all groups but we will include a covariate for the classification of risk of treatment failure (minimal or elevated). To evaluate whether the intensity of HCV treatment support also had any impact on HIV viral suppression outcomes, a covariate for the intensity of intervention received will also be included. In order to account for missing data due to loss-to-follow-up, we will use inverse-weighting methods.[97,98] Additional sensitivity analyses will vary the threshold for HIV viral suppression to account for blips, considering cutoffs of <200 copies/ml, <500 copies/ml and <1000 copies/ml.

15.7.2.3. Exploratory analysis.

Exploratory outcomes. These are described in the Statistical Analysis Plan.

Effect of delays in treatment completion on SVR. Additional exploratory analyses will evaluate the impact of non-adherence and delays in completing treatment on SVR. Initial analyses will incorporate data from all three arms. Two variables will be calculated: 1) the percentage of doses completed (as described above); and 2) days to treatment completion. While the scheduled course of treatment will be 84 days for most, participants will be instructed to take all of the doses prescribed (even if doses are missed and the total time for treatment completion extends beyond 84 days. In separate models, log-binomial regression will be used to estimate the association between 1) estimated adherence; and 2) days to treatment completion and SVR. These analyses will be combined across risk strata and treatment arm but these variables will be included as covariates. Additional analysis will be conducted exclusively among participants assigned to Arm 3 (high intensity support) where adherence data will be objectively collected using biometric data.

Estimation of heterogeneity in treatment effect and estimation of average treatment effect. Additional analyses will be completed to estimate heterogeneity in treatment effect and the average treatment effect for the primary (SVR) and secondary outcomes (treatment completion) defined above.

The average treatment effect will be determined in order to estimate the effect of the different support strategies in the overall population. Under the unbalanced randomization scenario that is planned, a prognostic score is intentionally created. This score lies between the causal pathway from the individual characteristics to the treatment assignment, thus introducing an "informed confounding", i.e., the causal relationship between treatment assignment and outcome is confounded by the prognostic score (i.e., individual's propensity for treatment failure). To estimate the unbiased, average treatment effect, given that there is information on how the prognostic score affects study arm allocation, the targeted randomization can be used to reweight the sample back to the initial sample as if the randomization allocation was equivalent to all levels of the prognostic score. That is, by using inverse probability of treatment weights, the relationship between the prognostic score and treatment assignment is removed to estimate the average treatment effect to provide answers about whether the high and moderate intensity interventions resulted in superior outcomes in the overall population (i.e., is high intensity support a superior intervention to standard of care in all PWID regardless of propensity for treatment failure?).

These analyses will seek to use information from the prognostic score and the observed data to identify the optimal threshold for assigning treatment support. That is, by assessing heterogeneity in treatment effect by level of prognostic score, we will potentially be able to identify a range of scores to assist in the decision of whether low, moderate, or high level of support would be most efficacious for individuals based upon the characteristics that determine their prognostic score. First, within the two strata defined by the prognostic score, there remains variability in the prognostic score. Therefore, we will evaluate the impact of the interaction between the prognostic score and the intensity of support received (low, medium and high intensity) on SVR and treatment completion rates in the full sample. The goal of this analysis will be to evaluate the heterogeneity of treatment effect *within* strata.

Of additional interest is identifying the heterogeneous treatment effect of the intensity of support received on SVR and secondary outcomes across the *entire distribution of* prognostic score (note that the prognostic score will be continuous). Therefore, by using the weighted (by inverse probability of treatment weights) study sample, the interaction between the prognostic score and intensity of support received on SVR and treatment completion rates can be examined across the entire study population. Specifically, a model will include the indicator variables for level of support, the main effect of the prognostic score, and the interaction term. The model will allow for non-linear relationship between prognostic score and outcomes and depict the estimated treatment effect graphically to determine the optimal cut-points of the prognostic score to assign low, medium and high intensity treatment support to maximize SVR.

Effect of heterogeneity of intervention effect by gender. It is of interest to examine whether the impact of the intervention varies by gender. We anticipate that power will be limited in these analyses since in many of the field sites, the number of women is negligible, consistent with the epidemiology of injection drug use in India. However, we will conduct stratified analyses to explore whether the effect of the level of treatment support varies by gender within strata of treatment nonadherence risk. We will also conduct the analyses of the average treatment effect stratified by gender.

16. DATA HANDLING AND RECORDKEEPING

16.1 Data Management Responsibilities

This study will be 7 field sites throughout India but will be coordinated by a single site, YRG CARE) in Chennai, Tamil Nadu, India with oversight from investigators at the Johns Hopkins Bloomberg School of Public Health and the Johns Hopkins School of Medicine. Investigators from Johns Hopkins and YRGCARE will oversee all aspects of the trial including participant recruitment, data collection, laboratory testing, biological sample storage, and data management. Additional details can be found in the **Data and Safety Monitoring Plan**.

16.2 Source Documents and Access to Source Data/ Documents

Source documents for this study are the eCRFs and the EHR which will be made available to the sites for data entry. The eCRFs and the EHR will be hosted online and copies will also be available on the laptop (in case of regions where the internet connectivity is limited). Additional details can be found in the **Data Safety and Monitoring Plan.**

16.3 Quality Control and Quality Assurance

16.3.1. Procedures to ensure the validity and integrity of the data

All field staff, interviewers, phlebotomists and clinicians who will come into contact with study participants will be required to complete research ethics and good clinical practice (GCP) training.

Lab technicians/phlebotomists at YRG CARE have undergone training on research ethics and good clinical laboratory practices (GCLP). The YRG CARE Infectious Disease Lab is certified by the *College of American Pathologists, United Kingdom National External Quality Assurance Scheme, and the Virologic Quality Assessment Program, US* and by the *AIDS Clinical Trials Group and Abbott Laboratories Inc, US* to perform HIV-1 genotypic resistance testing. GCLP are monitored by Johns Hopkins, Family Health International, and PPD.

Additional details can be found in the **Data Safety and Monitoring Plan**. Internal and external study monitors will implement routine quality management activities detailed in the **Study MOP**.

16.3.2. Procedures to guarantee the accuracy and completeness of the data

Our primary mode of data collection will be through the EHR at the ICCs and study specific eCRFs. Additional details can be found in the **Data Safety and Monitoring Plan**.

17. CLINICAL SITE MONITORING

Clinical site monitoring will include both internal and external monitoring.

17.1 Internal Site Monitoring

Internal monitoring will include annual site visits will be made by the PIs as well as quarterly visits from three monitors employed by YRGCARE. Details of these monitoring activities can be found in the **Data and Safety Monitoring Plan**.

17.2 External Site Monitoring

An independent monitor contracted by YRGCARE will conduct external monitoring assessments. Over the course of the trial, there will be three on-site monitoring visits and three remote monitoring visits for a total of two monitoring visits per year per site. Additional details can be found in the **Data and Safety Monitoring Plan**.

18. HUMAN SUBJECTS PROTECTIONS

18.1 Institutional Review Board/Ethics Committee

The protocol and all informed consent documents will be approved by the Institutional Review Boards of the Johns Hopkins School of Medicine in the US and the YRGCARE in Chennai, India. In addition, the study will be approved by the Indian Council of Medical Research and the Health Ministry Screening Committee. Any subsequent modifications will be reviewed and approved by both the Johns Hopkins and the YRGCARE IRBs. IRB continuing review and approval will be obtained from both the Johns Hopkins and YRGCARE IRBs once a year. If IRB approval expires or lapses, all ongoing research activities will stop unless the PIs determine that it is the best interests of already enrolled participants to continue their study-related activities. New participants will not be enrolled in the study until the IRB approval to continue the research is obtained.

18.2 Vulnerable Participants

18.2.1. Pregnant women and fetuses

Pregnant women will be excluded as described in **Section 14.2**. If a woman becomes pregnant while on treatment, the procedures are described in **Section 12.2.8**.

Pregnant women can continue to receive services at the clinical sites (ICCs).

18.2.2. Prisoners

It is possible that persons who are enrolled become prisoners during the course of the study. This means that they may become prisoners while they are taking HCV treatment. We do not have formal agreements in place to provide study treatment while participants are in prison. However, we will work with the prisons in each of the cities to establish agreements where possible. The goal will be to support study participants to complete their course of treatment while in prison by either delivering treatment through peers, family members and or other prison staff. However, we will not conduct any research activities while study participants are in prison. This means that intervention support activities will cease and no formal data collection will be conducted and study

visits will be classified as “missed” while participants are in prison. We will continue to track them so that when they are released we can reengage them in clinical care and study activities as appropriate.

18.2.3. Illiterate participants

Some of our research participants will be illiterate. As required by the JHMI and YRGCARE IRB, all informed consent documents will be read verbatim and participants who cannot sign will be asked to provide a thumb print.

18.3 Informed Consent

18.3.1. Informed consent process

Potentially eligible participants according to standard HCV treatment assessments in the ICCs will be asked to provide written informed consent prior to being screened for enrollment in the trial.

To obtain consent, participants will meet with a research staff member in a private area to discuss the research. Any study staff member who obtains informed consent from study participants will have completed requisite human subjects training. The research staff will present a brief overview of the study and what is being requested of the participant. If participants continue to express interest, the research staff will present the study in detail in conjunction with the informed consent script or document. Participants will be encouraged to ask questions during the consent process. Following this discussion, subjects will be asked comprehension questions to gauge the degree to which they have understood the study procedures. Participants will then be asked to provide a signature or thumbprint (if illiterate).

Consent documents will be approved by the JHU and YRGCARE IRBs. The rights and welfare of the participants will be protected by emphasizing to them that the availability of medical care will not be affected if they decline to participate in this study. In particular, receipt of services at ICCs is not conditioned upon participation in any aspect of the study.

18.3.2. Documentation of informed consent

Participants who provide written consent will be given a copy of the consent. In addition, a signed copy of the consent will be maintained in locked cabinets at each of the study field sites.

18.3.3. Stored samples and associated data considerations

Blood (serum and plasma) samples collected for this study that are not used for study related laboratory testing will be stored for 5 years after completion of the study. We will use these specimens for some planned analyses including HCV genotyping/sequencing which may be needed to differentiate between relapse and reinfection among participants failing to achieve SVR. We will also test for the presence of RAS in these specimens by sequencing the NS5A and NS5B regions. Stored specimens may also be used for ancillary analyses.

Specimen storage will be optional and there will be a designation on the written informed consent. Individuals may consent to participation in the study without agreeing to store their specimens.

The consent will be for broad use related to HIV and HCV. We will not be collecting samples to generate cell lines that would be needed for host genetic testing.

There will be no provision to recontact participants with results of ancillary testing that may be done with stored specimens.

18.4 Risks

Potential risks to participants include loss of confidentiality, minor discomfort from blood draw, embarrassment responding to questions about drug use and risk behaviors, anxiety from HCV and related tests. The likelihood of these risks is moderate and the potential seriousness is minor.

Loss of confidentiality, particularly regarding stigmatizing information or illegal behavior, is a potential risk to all participants. To minimize this risk among participants, in electronic databases, identifying information will be included in a minimal number of eCRFs that require this information. The majority of eCRFs will include only a unique study identification number. Data will be stored on an Secure Sockets Layer (SSL) certified server. In the ICCs, HIV and HCV counseling and testing will be offered to all clients. Trained counselors will deliver pre- and post-test counseling consistent with Indian guidelines. In addition, blood draws will be conducted by trained phlebotomists.

See package inserts (**Appendix 1**) for drug related risks.

18.5 Social Impact Events

Individuals enrolled in this study may experience personal problems resulting from the study participation. Such problems are termed social impact events. Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that participants may experience stigmatization or discrimination as a result of being perceived as being HIV- infected or HCV-infected at risk for HIV or HCV infection. For example, participants could be treated unfairly, or could have problems being accepted by their families and/or communities. Problems may also occur in circumstances in which study participation is not disclosed, such as impact on employment related to time taken for study visits.

In the event that a participant reports a social impact event, every effort will be made by study staff to provide appropriate assistance, and/or referrals to appropriate resources. Social impact events are documented and reviewed on a scheduled basis by the protocol team leadership with the goal of reducing their incidence and enhancing the ability of study staff to mitigate them when possible. In addition, social impact events will also be reported on regular DSM reports. Social impact events that are judged by the designee to be serious, unexpected, or more severe or frequent than anticipated, will be reported to the Study Manager and the local IRB promptly, or otherwise in accordance with the local IRB’s requirements.

18.6 Benefits

The direct benefit to participants is the free receipt of HCV RNA testing and HCV treatment with treatment adherence support, which are currently not available free of charge in all Indian states. This study also has the potential to provide benefit to the population at large if the study identifies the optimal support strategy to support PWID undergoing HCV treatment.

18.7 Compensation

Participations will be compensated 350 Indian Rupee (INR) (~$5.00 USD) for the study entry visit, on treatment visits and the SVR visit and 250 INR (~$3.50 USD) for post-treatment visits to ascertain reinfection and HIV viral suppression.

18.8 Participant Privacy and Confidentiality

All participant-related information including eCRFs, laboratory specimens, evaluation forms, reports, etc., will be kept strictly confidential. All paper records will be kept in a secure, double-locked location and only research staff will have access to the records. For electronic records, an encrypted cloud-based data collection storage system will be used. Trained interviewers will conduct face-to-face interviews with participants and enter responses directly onto a laptop computer or tablet. Information will be routed directly to a central server via a local network. Encrypted data will be stored on an SSL certified server. Access to data at the sites will be password protected with differential access per study staff. Human specimens (blood) will be labeled using study specific ID numbers only, with no personal identifying information on the tube or paperwork. Samples will be shipped under specified conditions and time frames to YRGCARE for laboratory testing. The biometric system that will be used generates a unique and reproducible hexadecimal code when the biometric is scanned or rescanned. The software does not store any identifiable images and hexadecimal codes cannot be back-converted to an image.

Only the field teams delivering care to participants will have access to identifying information of study participants. Any data that is sent to US investigators for analysis will be deidentified.

Upon request, participant records will be made available to the study sponsor, the sponsor's monitoring representative and applicable regulatory entities. U.S. government agencies, other local, US, and international regulatory entities, and companies that provide money to do the study and safety monitors may need to see participant information.

18.9 Certificates of Confidentiality

Certificates of confidentiality are not recognized by the Indian Government.

18.10 Critical Event Reporting

Critical events include unanticipated problems involving risks to participants or others, serious noncompliance, continuing noncompliance, suspension or termination of IRB approval and suspected research misconduct.

These will be reported to DAIDS and the JHU and YRGCARE IRBs within 14 days of the event coming to the PIs attention.

18.11 Communicable Disease Reporting

As per the standard of care in the ICCs (standard practice for the past five years), all new cases of HIV will be reported to the State AIDS Control Society and the National AIDS Control Organization. There is no standard reporting for HCV in India, but we will work with the National AIDS Control Organization to report cases if changes are made to this policy during the study period.

18.12 Incidental Findings

Any clinically significant findings that are discovered during the course of the study will be reported to study participants.

18.13 New Findings

If any study-relevant new findings are reported during the course of the study that may impact the willingness of participants to continue on study and/or willingness to join the study, the new findings will be discussed with study staff and the consent form will be revised and submitted to the relevant IRBs. Participants will be reconsented via a consent form that includes discussion of the new findings.

18.14 Study Discontinuation

The study may be discontinued at any time by the IRB or NIAID as part of their duties to ensure that research participants are protected.

18.15 Post-Trial Access

Not applicable.

18.16 Ancillary Benefits

As is required by the Government of India, if a person is injured as a result of being in the study s/he will be given immediate treatment of injuries as per YRGCARE's standard of care. The entire cost of health care and compensation due to study related injury or death will be covered by YRGCARE through "Clinical Trials Insurance."

1. In the case of an injury occurring to the clinical trial participant, he or she shall be given free medical management as long as required.

2. In case the injury occurring to the trial participant is related to the clinical trial, such participant shall also be entitled for financial compensation as per order of the Licensing Authority (The Drug Controller General of India) and the financial compensation will be over and above any expenses incurred on the medical management of the participant.

3. In the case of clinical trial related death of the participant, his/her nominee(s) would be entitled for financial compensation, as per the order of the Licensing Authority and the financial compensation will be over and above any expenses incurred on the medical management of the participant.

4. Financial compensation shall be paid by the Clinical Trial Insurance (New India Assurance Co. Ltd) if the death is due to the reasons specified under the Rule 122 DAB of the "Drugs and Cosmetics Rules, 1945" and as per the Order from the "Central Drugs Standard Control Organization."

18.17 Community Advisory Board and Other Relevant Stakeholders

Community advisory boards are already present in each of the study field sites as part of ongoing research activities and they will continue to be engaged throughout this protocol. Community meetings will occur quarterly.

19. ADMINISTRATIVE PROCEDURES

19.1 Protocol Registration

Not applicable.

19.2 Regulatory Oversight

Not applicable.

19.3 Study Implementation

Additional details can be found in the **Study MOP.**

19.4 ClinicalTrials.gov

This protocol will be registered in ClinicalTrials.gov.

20. PUBLICATION POLICY

See **Study Publication Policy**.

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