Direct-acting antiviral therapy and reinfection among people with chronic hepatitis C virus infection and recent injecting drug use in community-based settings

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Protocol Synopsis

Title	Direct-acting antiviral therapy and reinfection among people with chronic hepatitis C virus infection and recent injecting drug use in community-based settings
Protocol registration no.	**NCT03343925**
Background and rationale	In Australia, hepatitis C virus (HCV)-related morbidity and mortality have doubled in the past decade, with health care costs of $220 million per annum[1]. This is due to a large, ageing population with chronic infection (230,000), and low uptake of existing interferon-based therapy (1-2% per year) due to side-effects, and sub-optimal therapy efficacy. The majority of new (90%) and existing (80%) cases of HCV infection occur among people who inject drugs (PWID). In the community, 15-20% of current PWID report recent (last month) receptive needle/syringe sharing[2]. Qualitative research shows that decisions about sharing equipment are multi-factorial and can include issues ranging from service access (such as distance to service and opening hours), concerns about anonymity, perceptions that HCV is ubiquitous and unavoidable[3] to socially-located concerns that promote use of sterile equipment such as a desire to avoid "track marks"[4]. There is no research that examines sharing of injecting equipment in those with successful therapy in either community or prison settings. Increasing access to HCV therapy is a key objective of national and NSW Hepatitis C Strategies[5,6]. The advent of well-tolerated, simple, oral hepatitis C virus (HCV) regimens - direct acting antivirals (DAAs) – has the potential to transform this landscape. These are much shorter, tolerable treatment regimens with cure >95%, providing an opportunity to reverse the rising burden of advanced liver disease. From 1st March 2016, these highly efficacious HCV therapies have been listed on the Pharmaceutical Benefit Scheme, and people with recent injecting drug use are eligible to receive them. This is an important feature of the listing. In many countries, people who have not ceased injecting drug use are ineligible to receive DAA therapy[7], despite the fact that they comprise a significant proportion of HCV cases. Australia is therefore

poised to lead the world in the scale-up of new therapies to an extent that many countries with such exclusions will not be able to achieve.

This feature of DAA access also affords unique opportunities with respect to the implementation of treatment scale-up in community drug treatment clinics. Australia has good treatment coverage for people who are opioid dependent, with over 50% of opioid dependent people estimated to engage in opioid substitution therapy (OST) [8]. Community-based drug treatment clinics represent another logical venue for expansion of HCV care beyond existing tertiary HCV treatment centres [9,10].

Although response to DAA HCV therapy is high, lower responses have been observed among people with previous treatment experience[9], cirrhosis[9] and those with baseline or emergent resistance associated variants[10]. Such resistance associated variants can persist for up to two years after treatment[11], affect re-treatment options[12], and be transmitted to new hosts[13]. Further, PWID are likely to be exposed to multiple HCV infections as a result of ongoing high-risk behaviours and might commonly harbour mixed HCV infections (infection with two or more distinct viruses) [14]. Underlying mixed HCV infection can contribute to nonresponse during therapy[14], which has implications for DAA regimens that are preferentially active against specific viral genotypes or subtypes. These data argue for surveillance of HCV resistance and mixed HCV infection among PWID to resolve residual concerns regarding their clinical and public health significance.

Two systematic reviews assessing interferon-based therapy for PWID have demonstrated responses comparable to randomised controlled trials excluding PWID[15, 16]. These data have supported international recommendations for the management of HCV for PWID [17]. However, there are limited data on DAA therapy among recent PWID. As treatment is broadened to include more marginalised individuals, many clinicians are reluctant to treat HCV among PWID with recent injecting drug use with new DAA therapies. Major concerns include poor adherence/response, increased risk behaviour and HCV reinfection.

	A major concern is that ongoing injecting risk behaviours following DAA therapy in PWID will lead to HCV reinfection, reversing the benefits of cure. Ongoing risk behaviours following successful HCV therapy may lead to reinfection and compromised treatment outcomes[14]. In a systematic review and meta-analysis of HCV reinfection among PWID performed by the investigators, the pooled estimate of re-infection was 2.2/100 p-yrs (95% CI, 0.9-6.1) overall and 6.4/100 p-yrs (95% CI, 2.5-16.7) among individuals who reported injecting drug use post-SVR[16]. The one study of HCV reinfection post-therapy in prison performed to date was small (n=74), retrospective, and did not assess the rate of HCV reinfection[18]. Studies of reinfection following HCV therapy are limited by small sample sizes, retrospective study designs, incomplete follow-up, and a lack of sensitive methods to detect reinfection. Further, there are no data on HCV reinfection among recent PWID treated with DAAs. Although DAA therapy could limit HCV-related disease burden, as treatment is broadened to include more marginalised individuals, many clinicians are reluctant to treat HCV among recent PWID, given concerns about poor adherence (and lower response to therapy), increased risk behaviours (due to the ease and high cure rates of DAA HCV therapy) and HCV reinfection (thereby reversing cure). However, no data exist on the extent to which this should be a concern. Given that DAA HCV therapy is highly expensive, we urgently need data on the magnitude of risk for, and predictors of, HCV reinfection. It is also unclear whether PWID treated in these two settings will vary in their response to DAA therapy and risk for reinfection. The investigators have an excellent track record of conducting high quality cohort studies and clinical trials among PWID in the community[19-23] and prison[24], with high participant retention in follow-up. The investigators have developed a network of clinical sites providing HCV care in nine community-based drug treatment clinics[20, 25]. In SHARP-C the investigators will explore the risk of HCV reinfection and treatment efficacy among recent PWID with chronic HCV and recent injecting drug use.

Study objectives	**Primary Objective** To evaluate the incidence of HCV reinfection following successful DAA therapy among people with chronic HCV infection and recent injecting drug use. **Secondary Objectives** 1) To evaluate the proportion of participants with undetectable HCV RNA at 12 weeks post end of treatment (SVR12) following DAA HCV therapy among PWID with chronic HCV infection and recent injecting drug use; 2) To evaluate the proportion of participants who complete treatment; 3) To evaluate the proportion of participants with undetectable HCV RNA at the end of treatment. **Exploratory Objectives** 1) To evaluate demographic, clinical and virological predictors of HCV reinfection; 2) To evaluate demographic, clinical and virological factors associated with SVR12; 3) To evaluate injecting risk behaviours during and following HCV treatment; 4) To evaluate HCV phylogenetic clustering and molecular epidemiology; 5) To evaluate the prevalence of resistance associated substitutions; 6) To evaluate the immunovirological changes occurring in the context of treatment, following treatment, and in the setting of post-treatment re-viremia including reinfection and relapse; 7) To determine the sensitivity and specificity of the Xpert® HCV Viral Load assay for HCV RNA detection in samples collected by finger-stick capillary whole-blood
Participant population	Participants will be recruited from hospital-based HCV clinics and community-based drug treatment clinics. *Inclusion criteria* 1) Participants have voluntarily signed the informed consent form.

	2) Be ≥18 years of age on day of signing informed consent form. 3) Have chronic HCV infection. 4) Recent injecting drug use (previous 6 months). 5) Eligible for DAA therapy as per the government criteria 6) HIV-1 infected participants enrolled in the study must meet the following criteria: a) Have HIV infection documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry (Baseline) and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 p24 antigen, or plasma HIV-1 RNA viral load. b) Be on HIV Antiretroviral Therapy (ART) for at least 4 weeks prior to study entry using an ART regimen that is allowable with the intended DAA regimen as determined by the current PI and the Liverpool drug interaction website (http://www.hiv-druginteractions.org/) OR be naive to treatment with any antiretroviral therapy (ART) with a baseline CD4 count of >200 and have no plans to initiate ART treatment while participating in this study and through to at least Follow-up Week 4. ***Exclusion criteria*** 1) The participant must be excluded from participating in the trial if the subject is unable or unwilling to provide informed consent or abide by the requirements of the study.
Study design	A prospective, observational cohort design will be used to enrol PWID with chronic HCV and recent injecting drug use (injecting drug use in the previous six months) from an existing network of hospital–based and community clinics. Persons with chronic HCV infection will receive direct acting antiviral treatment.
Treatment of participants	Participants will be treated with a government approved DAA drug regimen which will be prescribed as appropriate for the participants fibrosis stage, HCV genotype and previous treatment experience at the discretion of the treating clinician.

Study procedures	Refer to the Schedule of Assessments and Study Procedures (Section 7)
Statistics	***Primary Objective:*** To evaluate the incidence of HCV reinfection following successful DAA therapy among people with chronic HCV infection and recent injecting drug use. *Statistical analysis:* Rates of HCV reinfection will be calculated using person-time of observation. The estimated date of reinfection will be calculated as the midpoint between the dates of the last undetectable HCV RNA test and the first detectable HCV RNA test at the time of HCV reinfection. Time at risk will commence at the date of undetectable HCV RNA at end of treatment and end at the first of estimated date of re-infection, death, loss-to-follow up or end of study. Confidence intervals for rates will be calculated using a Poisson distribution. Cox proportional hazards analyses (or other appropriate regression models) will be used to estimate crude and adjusted hazard ratios and corresponding 95% CI to evaluate factors associated with reinfection. Factors hypothesised to be associated with reinfection include demographic factors (age, sex), injecting behaviours (recent injecting drug use, daily injecting, type of drug injected, injecting equipment borrowing), use of needle and syringe programs, and opioid substitution treatment with time-updated co-variates. *Sample Size:* Overall, based on previous reports of HCV reinfection among recent PWID[30], and assuming loss to follow-up is 20% per year, it is estimated that the overall reinfection rate will be 8/100 p-yrs (95%CI 5.7-10.7; 478 p-yrs of follow-up; 38 reinfections). Overall (225 with successful therapy, 38 reinfections), we will have 80% power to detect a hazards ratio (HR) of 2.47 or greater (with alpha=0.05) for a variable 50% prevalent (e.g. ongoing injecting drug use).

	<u>Secondary Objectives</u>: 1) To evaluate the proportion of participants with undetectable HCV RNA at 12 weeks post end of treatment (SVR12) following DAA HCV therapy among PWID with chronic HCV infection and recent injecting drug use; 2) To evaluate the proportion of participants who complete treatment; 3) To evaluate the proportion of participants with undetectable HCV RNA at the end of treatment

Schedule of Assessments

Assessment / Procedure	Baseline	ETR	Follow-up (weeks from variable ETR)												
Study weeks	**0**	**Variable**	**Weeks from variable ETR**	**12 (SVR12)**	**24 (SVR24)**	**36 (FU1)**	**48 (FU2)**	**60 (FU3)**	**72 (FU4)**	**84 (FU5)**	**96 (FU6)**	**108 (FU7)**	**120 (FU8)**	**132 (FU9)**	**144 (FU10)**
Visit Window (Days)		**+/- 14**		**+/- 14**	**+/- 14**	**+/- 14**	**+/- 14**	**+/- 14**	**+/- 14**	**+/- 14**	**+/- 14**	**+/- 14**	**+/- 14**	**+/- 14**	**+/- 14**
Informed consent, medical history	x														
Behavioural survey	x														
Abbreviated behavioural survey		x		x	x	x	x	x	x	x	x	x	x	x	x
Health outcomes survey (EQ-5D-5L)	x	x		x	x	x	x	x	x	x	x	x	x	x	x
HCV RNA testing (Local Laboratory)		x[a]		x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]
HCV-RNA testing (Finger-stick point of care testing)	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Research Sample (10 mL EDTA plasma and Whole Blood)	x[b]	x[a]		x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]

[a] If the HCV RNA point of care test is positive or invalid or if the participant is suspected of relapse or reinfection, [b] 4ml whole Blood and 20mL EDTA at Baseline only

Schedule of Assessments - participants with post-treatment recurrence of viremia

Participants who return a positive HCV RNA finger-stick point of care test during the follow up period will be considered to have post-treatment recurrence of viremia. Participants with post-treatment recurrence of viremia following DAA treatment will also have the following tests performed at certain time points.

Assessment/Procedure				
Study Visit	**Re-viremia baseline**	**RFU1**	**RFU2**	**RFU3**
Weeks from re-viremia baseline		**2**	**4**	**8**
Visit window (days)		**+/- 14**	**+/- 14**	**+/- 14**
HCV-RNA testing (Finger-stick point of care testing)		x	x	x
Research sample (EDTA plasma) (10mL)		x	x	x
HCV sequencing (tested at central lab using research sample collected at baseline) [a]	x			

[a] For participants with post -treatment recurrence of viremia HCV sequencing will also be carried out on the research sample (10mL EDTA) that is collected at baseline of the main study

1. Background and rationale

In Australia, hepatitis C virus (HCV)-related morbidity and mortality have doubled in the past decade, with health care costs of $220 million per annum[1]. This is due to a large, ageing population with chronic infection (230,000), and low uptake of existing interferon-based therapy (1-2% per year) due to side-effects, and sub-optimal therapy efficacy. The majority of new (90%) and existing (80%) cases of HCV infection occur among people who inject drugs (PWID).

In the community, 15-20% of current PWID report recent (last month) receptive needle/syringe sharing[2]. Qualitative research shows that decisions about sharing equipment are multi-factorial and can include issues ranging from service access (such as distance to service and opening hours), concerns about anonymity, perceptions that HCV is ubiquitous and unavoidable[3] to socially-located concerns that promote use of sterile equipment such as a desire to avoid "track marks"[4]. There is no research that examines sharing of injecting equipment in those with successful therapy in either community or prison settings.

Increasing access to HCV therapy is a key objective of national and NSW Hepatitis C Strategies[5,6]. The advent of well-tolerated, simple, oral hepatitis C virus (HCV) regimens - direct acting antivirals (DAAs) – has the potential to transform this landscape. These are much shorter, tolerable treatment regimens with cure >95%, providing an opportunity to reverse the rising burden of advanced liver disease. From 1st March 2016, these highly efficacious HCV therapies have been listed on the Pharmaceutical Benefit Scheme, and people with recent injecting drug use are eligible to receive them. This is an important feature of the listing. In many countries, people who have not ceased injecting drug use are ineligible to receive DAA therapy[7], despite the fact that they comprise a significant proportion of HCV cases. Australia is therefore poised to lead the world in the scale-up of new therapies to an extent that many countries with such exclusions will not be able to achieve.

This feature of DAA access also affords unique opportunities with respect to the implementation of treatment scale-up in community drug treatment clinics. Australia has good treatment coverage for people who are opioid dependent, with over 50% of opioid dependent people estimated to engage in opioid substitution therapy (OST) [8]. Community-based drug treatment clinics represent another logical venue for expansion of HCV care beyond existing tertiary HCV treatment centres [9,10].

Although response to DAA HCV therapy is high, lower responses have been observed among people with previous treatment experience[9], cirrhosis[9] and those with baseline or emergent resistance associated variants[10]. Such resistance associated variants can persist for up to two years after treatment[11], affect re-treatment options[12], and be transmitted to new hosts[13]. Further, PWID are likely to be exposed to multiple HCV infections as a result of ongoing high-risk behaviours and might commonly harbour mixed

HCV infections (infection with two or more distinct viruses) [14]. Underlying mixed HCV infection can contribute to nonresponse during therapy[14], which has implications for DAA regimens that are preferentially active against specific viral genotypes or subtypes. These data argue for surveillance of HCV resistance and mixed HCV infection among PWID to resolve residual concerns regarding their clinical and public health significance.

Two systematic reviews assessing interferon-based therapy for PWID have demonstrated responses comparable to randomised controlled trials excluding PWID[15, 16]. These data have supported international recommendations for the management of HCV for PWID [17]. However, there are limited data on DAA therapy among recent PWID. As treatment is broadened to include more marginalised individuals, many clinicians are reluctant to treat HCV among PWID with recent injecting drug use with new DAA therapies. Major concerns include poor adherence/response, increased risk behaviour and HCV reinfection.

A major concern is that ongoing injecting risk behaviours following DAA therapy in PWID will lead to HCV reinfection, reversing the benefits of cure. Ongoing risk behaviours following successful HCV therapy may lead to reinfection and compromised treatment outcomes[14]. In a systematic review and meta-analysis of HCV reinfection among PWID performed by the investigators, the pooled estimate of re-infection was 2.2/100 p-yrs (95% CI, 0.9-6.1) overall and 6.4/100 p-yrs (95% CI, 2.5-16.7) among individuals who reported injecting drug use post-SVR[16]. The one study of HCV reinfection post-therapy in prison performed to date was small (n=74), retrospective, and did not assess the rate of HCV reinfection[18]. Studies of reinfection following HCV therapy are limited by small sample sizes, retrospective study designs, incomplete follow-up, and a lack of sensitive methods to detect reinfection. Further, there are no data on HCV reinfection among recent PWID treated with DAAs.

Although DAA therapy could limit HCV-related disease burden, as treatment is broadened to include more marginalised individuals, many clinicians are reluctant to treat HCV among recent PWID, given concerns about poor adherence (and lower response to therapy), increased risk behaviours (due to the ease and high cure rates of DAA HCV therapy) and HCV reinfection (thereby reversing cure). However, no data exist on the extent to which this should be a concern. Given that DAA HCV therapy is highly expensive, we urgently need data on the magnitude of risk for, and predictors of, HCV reinfection. It is also unclear whether PWID treated in these two settings will vary in their response to DAA therapy and risk for reinfection.

The investigators have an excellent track record of conducting high quality cohort studies and clinical trials among PWID in the community[19-23] and prison[24], with high participant retention in follow-up. The investigators have developed a network of clinical sites providing HCV care in nine community-based drug treatment clinics[20, 25]. In SHARP-C the investigators will explore the risk of HCV reinfection and treatment efficacy among recent PWID with chronic HCV and recent injecting drug use.

2. Hypotheses

Primary Hypothesis

The incidence of HCV reinfection following successful DAA therapy will be <8 per 100 person years among people with current injecting drug use.

3. Study objectives

Primary Objective

To evaluate the incidence of HCV reinfection following successful DAA therapy among people with chronic HCV infection and recent injecting drug use.

Secondary Objectives

1) To evaluate the proportion of participants with undetectable HCV RNA at 12 weeks post end of treatment (SVR12) following DAA HCV therapy among PWID with chronic HCV infection and recent injecting drug use;
2) To evaluate the proportion of participants who complete treatment;
3) To evaluate the proportion of participants with undetectable HCV RNA at the end of treatment.

Exploratory Objectives

1) To evaluate demographic, clinical and virological predictors of HCV reinfection;
2) To evaluate demographic, clinical and virological factors associated with SVR12;
3) To evaluate injecting risk behaviours during and following HCV treatment;
4) To evaluate HCV phylogenetic clustering and molecular epidemiology;
5) To evaluate the prevalence of resistance associated substitutions;
6) To evaluate the immunovirological changes occurring in the context of treatment, following treatment, and in the setting of post-treatment re-viremia including reinfection and relapse;
7) To determine the sensitivity and specificity of the Xpert® HCV Viral Load assay for HCV RNA detection in samples collected by finger-stick capillary whole-blood;

4. Participant population

Participants will be recruited from hospital-based HCV clinics and community-based drug treatment clinics in Australia, New Zealand and Canada

Inclusion criteria

1) Participants have voluntarily signed the informed consent form.
2) Be ≥18 years of age on day of signing informed consent form.
3) Have chronic HCV infection.
4) Recent injecting drug use (previous 6 months).
5) Eligible for DAA therapy as per the government criteria

6) HIV-1 infected participants enrolled in the study must meet the following criteria:

c) Have HIV infection documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry (Baseline) and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 p24 antigen, or plasma HIV-1 RNA viral load.

d) Be on HIV Antiretroviral Therapy (ART) for at least 4 weeks prior to study entry using an ART regimen that is allowable with the intended DAA regimen as determined by the current PI and the Liverpool drug interaction website (http://www.hiv-druginteractions.org/) OR be naive to treatment with any antiretroviral therapy (ART) with a baseline CD4 count of >200 and have no plans to initiate ART treatment while participating in this study and through to at least Follow-up Week 4.

Exclusion criteria

1) The participant must be excluded from participating in the trial if the subject is unable or unwilling to provide informed consent or abide by the requirements of the study.

5. Study design

Main study

The primary objective of this project is to evaluate the incidence of HCV reinfection for up to three years following successful DAA therapy among PWID with recent injecting drug use. The secondary objective is to evaluate the proportion of patients with undetectable HCV RNA at 12 weeks post end of treatment (SVR12) following therapy with DAA among PWID with recent injecting drug use and chronic HCV infection and evaluate demographic and clinical predictors of non-response.

A prospective, observational cohort design will be used to enrol PWID with chronic HCV and recent injecting drug use (injecting drug use in the previous six months) from an existing network of hospital–based and community clinics. Persons with chronic HCV infection will receive direct acting antiviral treatment.

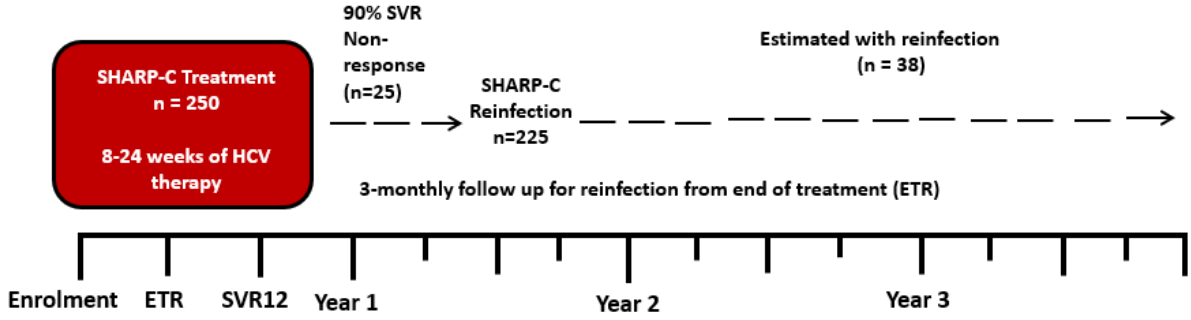

Figure 1: SHARP-C main study schema

Post-treatment recurrence of viremia

Participants who have a positive HCV RNA point of care test during the follow up period will be considered to have post-treatment recurrence of viremia. All patients identified as having post-treatment recurrence of viremia will have an increased follow up schedule for 8 weeks before returning to the standard follow up schedule. Participants once identified as having recurrent viremia will be followed intensely for 8 weeks as per the post-treatment recurrence of viremia schedule of assessments. Once the participant has completed 8 weeks follow up they will continue with 3 monthly follow up visits as per the standard schedule of assessments.

Patients may be offered retreatment with government approved DAA drug regimens. The decision to re-treat as well as the regimen and duration will be determined by the treating clinician according to government prescribing guidelines.

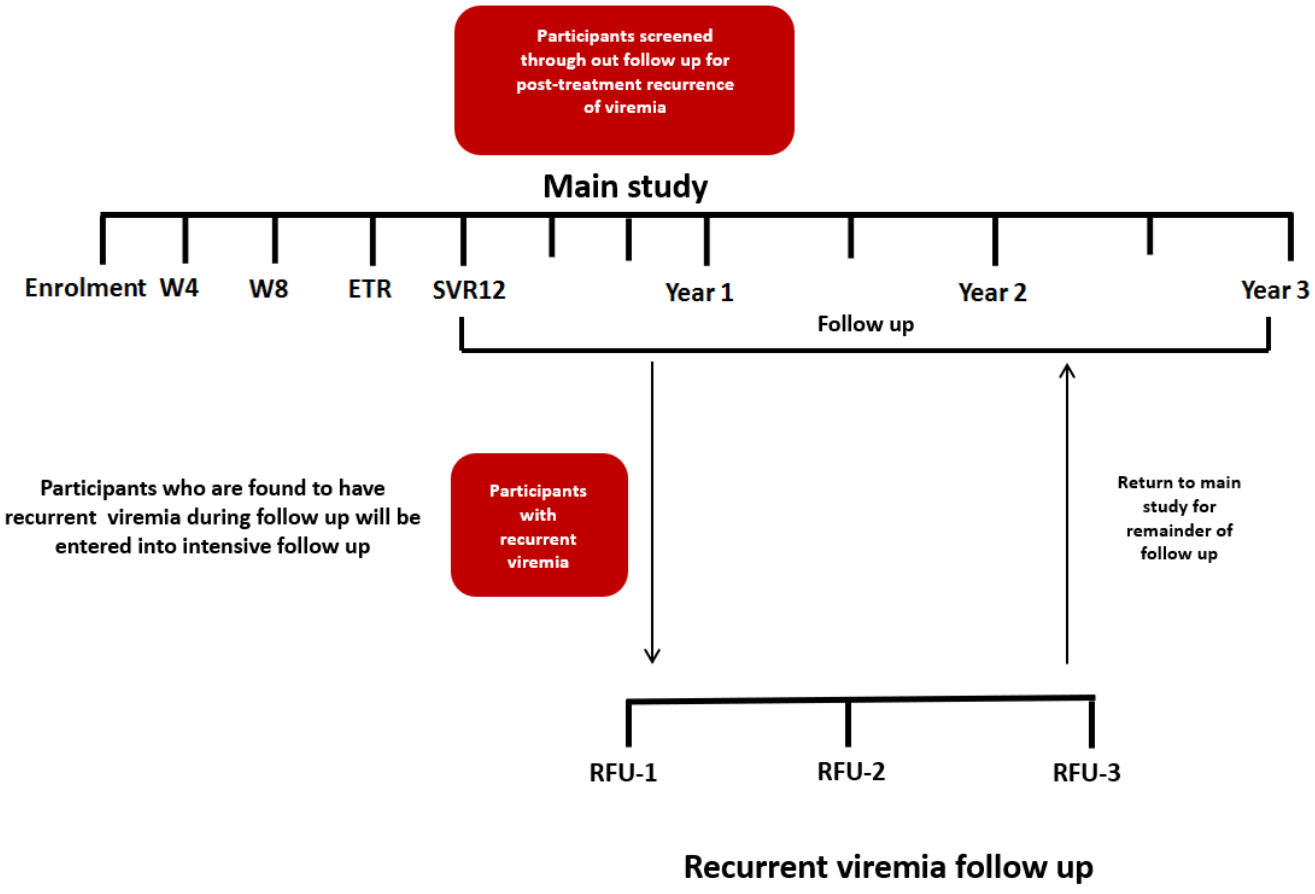

Figure 2: SHARP-C post-treatment recurrence of viremia schema

6. Treatment of participants

A total of 250 participants will be enrolled with chronic HCV, recent injecting drug use (past 6 months) and initiating DAA HCV therapy. Participants will be seen in hospital-based HCV and community-based drug treatment clinics.

Participants will be treated with a government approved DAA drug regimen which will be prescribed as appropriate for the participants fibrosis stage, HCV genotype and previous treatment experience at the discretion of the treating clinician.

6.1 Dosage and administration

Study drug is not being provided in this study as a government approved DAA regimen is being utilised.

6.2 Prior and concomitant medication

The treating clinician is responsible for assessing and managing the use of concomitant medications in line with the DAA regimen selected.

7. Study procedures

7.1 Visits and Procedures – main study

The following assessments must be conducted at study visits as per the schedule of assessments:

Finger-stick point of care testing HCV RNA testing (POC)	At all study visits. This point of care test will be performed using the Xpert® HCV Viral Load assay on the Gene Xpert® II machine.
Questionnaires	Behavioural survey, abbreviated behavioural survey and EQ-5D-5L
Research sample	20mL EDTA and 4mL whole blood at baseline. 10mL EDTA at other study visits if the HCV RNA point of care test is positive or invalid. 10mL EDTA at re-viremia follow up visits.
HCV sequencing (tested at Central lab using research sample after BSL)	For relapse and reinfection as needed.
HCV RNA testing (local laboratory)	Completed if the point of care test is positive or invalid.

The study physician is responsible for the treatment and monitoring of participants and their care. It is recommended that the following assessments are conducted as part of standard treatment monitoring, however this is at the physician's discretion. Any results that are generated from these assessments will be collected as part of the study data.

- Fibroscan or APRI value – within 12 months prior to baseline

The following assessments and procedures must be performed at each visit as specified below.

Baseline visit (Week 0)

- Informed consent
- Medical history
- Study questionnaires (Behavioural and EQ-5D-5L)
- HCV RNA (Finger-stick point of care testing)
- Research sample (20mL EDTA plasma & 4mL whole blood)
- HCV Sequencing (will be performed on the baseline research sample if re-viremia is detected at study follow up visits)

End of Treatment (ETR) – Variable (will depend on selected treatment regimen) (+/-14 days)

- Study questionnaires (Abbreviated Behavioural and EQ-5D-5L)
- HCV RNA (Finger-stick point of care testing)
- Research sample (EDTA plasma) (Only if the HCV RNA point of care test is positive or invalid)
- HCV RNA testing (Local Laboratory) (Only if the HCV RNA point of care test is positive or invalid)

Post Treatment Follow-up Visits

Post Treatment Week 12 (SVR12) – 12 weeks from ETR (+/- 14 days)

- Study questionnaires (Abbreviated Behavioural and EQ-5D-5L)
- HCV RNA (Finger-stick point of care testing)
- Research sample (EDTA plasma)) (Only if the HCV RNA point of care test is positive or invalid)
- HCV RNA testing (Local Laboratory) (Only if the HCV RNA point of care test is positive or invalid)

Post Treatment – SV24 (24 weeks post ETR), FU1 (36 weeks post ETR), FU2 (48 weeks post ETR), FU3 (60 weeks post ETR), FU4 (72 weeks post ETR), FU5 (84 weeks post ETR), FU6 (96 weeks post ETR), FU7 (108 weeks post ETR), FU8 (120 weeks post ETR), FU9 (132 weeks post ETR), FU10 (142 weeks post ETR) (+/- 14 days)

- Study questionnaires (Abbreviated Behavioural and EQ-5D-5L)
- HCV RNA (Finger-stick point of care testing)
- Research sample (EDTA plasma)) (Only if the HCV RNA point of care test is positive or invalid)
- HCV RNA testing (Local Laboratory) (Only if the HCV RNA point of care test is positive or invalid)

All participants who have suspected post treatment recurrence of viremia will have the following data and samples collected in addition to standard of care.

7.2 Visits and procedures – Participants with post-treatment recurrence of viremia

Re-viremia baseline

- HCV RNA sequencing (Tested at the central laboratory using the research sample collected at baseline)

Re-viremia follow-up – RFU1 (2 weeks post re-viremia baseline), RFU2 (4 weeks post re-viremia baseline) and RFU3 (8 weeks post re-viremia baseline)

- HCV RNA (Finger-stick point of care testing)
- Research sample (EDTA plasma)

7.3 Study Questionnaires

All subjects will undertake a number of study questionnaires at baseline, and selected follow-up visits.

The Behavioural Questionnaire

The study staff will assist participants to complete this questionnaire. The behavioural survey will collect information on the following:

- Demographics
- HIV and drug treatment history
- Drug and alcohol use
- Treatment acceptance and willingness (prior to treatment commencement only)
- Injecting risk behaviours (including information about injecting sharing partners and equipment sharing)

An abbreviated behavioural questionnaire (follow-up) will be administered at subsequent time points during the study.

Health Outcomes Survey (EQ-5D-5L)

The EQ-5D-5L health questionnaire provides a simple descriptive profile and a single index value for health status. This information can then be translated into a health utility, which can be used for cost-effectiveness analyses.

8. Recording and reporting Adverse Events (AEs)

The medications for this study are government approved DAA regimens. Adverse events and adverse drug reactions will be reported to the relevant government agency as per standard practice for government approved medications. Only deaths will be reported as detailed below.

8.1 Reporting deaths

All deaths should be reported within TWO (2) WORKING DAYS of becoming aware of the event to the Kirby Institute by fax or email using the SHARP-C deaths reporting form. Reports should be followed promptly by detailed, written follow-up reports when all information is not included in the initial report. Follow up reports should include all supporting documentation i.e. autopsy reports, as appropriate. Follow-up reports should be reported within TWO (2) WORKING DAYS also. The immediate and follow up reports should identify participants by unique code numbers assigned to study participants rather than personal identification.

Death reports must be submitted to **the Kirby Institute:**

Kirby Institute: Fax: +61 2 9385-9214.

sharp-c@kirby.unsw.edu.au

9. Packaging, labeling, storage and accountability of clinical trial supplies

Study drug is not being provided in this study. Government approved DAA medication will be used and will be dispensed and stored according to government regulations.

10.Biological samples

10.1 Laboratory supplies and sample processing

Laboratory supplies for collection of research specimens (plasma and whole blood – all sites and PBMCS – sub-study sites only) will be supplied by the Kirby Institute.

The following blood samples will be collected at time points specified in the schedule of assessments:

1. 10 mL EDTA plasma for HCV RNA testing and future HCV related research (20 mL will be collected at baseline visit);
2. 4mL whole blood for human genomic DNA analysis collected at the baseline visit only.

Samples will be collected by sites and then processed and stored at -70°C or below at the site local laboratory for bulk shipment to the Kirby Institute laboratory. Detailed sample processing instructions will be provided in the laboratory manual.

EDTA plasma samples will be used for study endpoint analysis. HCV viral load will be measured using in-house and commercial assays. Sequencing of the viral genome will also be performed as a more accurate means of genotyping. Data generated from the sequencing may also be used to distinguish relapse from reinfection and to examine the prevalence of mixed infection. Whole blood samples will be used to examine host factors associated with viral clearance, including but not limited to HLA type, IL28-B, , IP-10 , and other biomarkers.

Sequencing

Sanger sequencing will be performed on all participants with HCV RNA relapse or reinfection in post treatment follow up to distinguish HCV reinfection from viral relapse (detectable HCV RNA following HCV virological suppression). Complementary RNA will be generated using SuperScript® VILO™ cDNA Synthesis Kit (Life Technologies, Carlsbad, CA) with random hexamers. Sequencing of NS5A will be performed on all

participants. A fragment of the HCV genome covering Core, Envelope-1, hypervariable region-1 and beginning of Envelope-2 (E2) will be amplified using a method previously described. Sequencing of NS3/4, NS5A, NS5B, and full-length next generation sequencing may also be performed. Purified amplicons will be sequenced using the Sanger method and sequence chromatograms processed using RECall: a fully automated sequence analysis pipeline. Subtypes will be determined using the Oxford HCV Automated Subtype Tool. Reverse transcription, PCR and sequencing reaction and thermal cycling conditions will be performed as previously described. Further, Sanger sequencing and next generation sequencing will be performed among samples with persistent infection at risk of HCV mixed infection (e.g. treatment non-response).

HCV RNA point of Care testing

Point of care testing for HCV RNA detection will be performed at each visit using the Xpert® HCV Viral Load assay for samples collected by finger-stick capillary whole-blood as described below.

The capillary whole-blood sample is collected from participants via a finger-stick [MiniCollect® Safety Lancet (Order Number 450429), Greiner Bio-One, Monroe, Frickenhausen, Germany] using procedures recommended by the World Health Organization[31] and collected into a 100µL minivette collection tube [Minivette® POCT 100µl (Order number 17.2111.100), Sarstedt, Nümbrech, Germany]. The Xpert® HCV Viral Load assay is being evaluated as part of this study and is therefore only being used for research purposes, not for diagnostic purposes. As this assay is only being used for research purposes the results and a positive HCV RNA or invalid point of care test should be confirm by a local lab hepatitis C HCV RNA test the Xpert® HCV Viral Load assay will not be given to participants.

10.2 Shipping of biological samples

Samples must only be shipped to the Kirby Institute laboratory on the instruction from the Study Coordinator.

It is the responsibility of each site Principal Investigator to ensure that all site staff handling, packaging, and/or shipping biological samples understand and comply with International Air Transport Association (IATA) regulations relating to the handling and shipping of hazardous goods and/or diagnostic specimens.

10.3 Future use of biological samples

After the samples have been analysed for the study endpoints as specified in the protocol, remaining samples will be stored for use in future Human Research Ethics Committee approved hepatitis C related research. Samples will be stored until all of the samples have been used up or the sample is no longer viable. Additional consent will not be sought for this storage and future use. It is not optional. Subjects

not wishing to have their samples stored or used in future hepatitis C related research will not be eligible to participate in this study.

11. Statistics

The statistical team and investigators at the Kirby Institute will be responsible for analysing the study data.

Primary Objective:

To evaluate the incidence of HCV reinfection following successful DAA therapy among people with chronic HCV infection and recent injecting drug use.

Hypothesis 1.1: The incidence of HCV reinfection following successful DAA therapy will be <8 per 100 person- yrs among people with recent injecting drug use.

Hypothesis 1.2: HCV reinfection will be associated with ongoing daily injecting drug use, and needle and syringe borrowing, and the treatment in the prison. OST and high-coverage access to needle and syringes will be associated with reduced HCV reinfection.

Outcome: Incidence of HCV reinfection following successful DAA therapy.

Statistical analysis: Rates of HCV reinfection will be calculated using person-time of observation. The estimated date of reinfection will be calculated as the midpoint between the dates of the last undetectable HCV RNA test and the first detectable HCV RNA test at the time of HCV reinfection. Time at risk will commence at the date of undetectable HCV RNA at end of treatment and end at the first of estimated date of re-infection, death, loss-to-follow up or end of study. Confidence intervals for rates will be calculated using a Poisson distribution.

Cox proportional hazards analyses (or other appropriate regression models) will be used to estimate crude and adjusted hazard ratios and corresponding 95% CI to evaluate factors associated with reinfection. Factors hypothesised to be associated with reinfection include demographic factors (age, sex), injecting behaviours (recent injecting drug use, daily injecting, type of drug injected, injecting equipment borrowing), use of needle and syringe programs, and opioid substitution treatment with time-updated co-variates.

Sample Size: Overall, based on previous reports of HCV reinfection among recent PWID[30], and assuming loss to follow-up is 20% per year, it is estimated that the overall reinfection rate will be 8/100 p-yrs (95%CI 5.7-10.7; 478 p-yrs of follow-up; 38 reinfections). Overall (225 with successful therapy, 38reinfections), we will have 80% power to detect a hazards ratio (HR) of 2.47 or greater (with alpha=0.05) for a variable 50% prevalent (e.g. ongoing injecting drug use).

Secondary Objectives:

4) To evaluate the proportion of participants with undetectable HCV RNA at 12 weeks post end of treatment (SVR12) following DAA HCV therapy among PWID with chronic HCV infection and recent injecting drug use;
5) To evaluate the proportion of participants who complete treatment;
6) To evaluate the proportion of participants with undetectable HCV RNA at the end of treatment

Hypothesis 2.1: Reduced response to DAA therapy among recent PWID will be predicted by previous treatment experiences, cirrhosis, baseline mixed HCV infection and resistance associated substitutions.

Outcome: The primary endpoint for this aim is the proportion of participants with a treatment response (measured by SVR, undetectable HCV RNA 12 weeks after the completion of therapy).

Statistical analysis: The proportion of people with a response to HCV therapy will be evaluated. Factors associated with treatment response (as measured SVR) will be assessed by univariate and multivariate logistic regression analyses. Factors hypothesised to be associated with response to DAA therapy are: injecting behaviours (recent injecting drug use prior to and during treatment and type of drug injected), clinical factors (opioid substitution treatment, HCV regimen, fibrosis stage), and virological factors (HCV genotype, baseline mixed HCV infection, presence of resistance associated variants).

Sample size: Assuming an overall SVR of 90% (225 of 250), the 95% confidence intervals (95%CI) around this estimate will be 86.0 to 92.8%. This study will have robust power to examine the effect of treatment setting on SVR: e.g. 80% power to detect an odds ratio of 1.87 or greater (alpha=0.05) for a variable that is 50% prevalent (i.e. community vs. prison).

Collateral research

Objective: To evaluate injecting behaviours and injecting cessation following successful DAA therapy.

Hypothesis: Daily injecting drug use and needle and syringe borrowing will decrease following the initiation of HCV therapy.

Outcome: The primary endpoint for this aim is recent (past month) daily injecting drug use. Secondary endpoints will include the number of days injecting in the past month, recent (past month) injecting drug use, needle/syringe borrowing, injecting equipment borrowing, attitudes towards reinfection risk, non-injecting drug use, and opioid substitution therapy.

Statistical analysis: The proportions of individuals reporting behavioural outcomes will be assessed among all individuals longitudinally at all study visits. To account for loss to follow-up and the correlated nature of successive responses among participants, Generalised Estimating Equations (GEE) will be used to evaluate the impact of time in the study on all outcomes. Unadjusted and adjusted GEE models will be specified using a binomial family function, a logit link and an exchangeable correlation structure. Odds ratios with corresponding 95%CIs and p-values will be calculated. Variables hypothesised to be associated with behavioural outcomes will be evaluated using GEE analysis including sociodemographic factors (age, sex, housing), access to harm reduction services (OST and high-coverage NSP), and treatment setting (community vs. prison).

Sample Size: In the overall cohort, this study will have 80% power to detect a significant decrease in daily injecting from 50% to 42% over the study period. GEE models will further improve power and account for the correlated nature of successive visits among participants.

12. Data collection, source documents and record retention

The Principal Investigator and the institution where the study will be conducted will permit study-related monitoring, audits, ethics committee review and regulatory inspection providing direct access to source documents.

Data will be collected on study specific electronic or paper copy case record forms. The Principal Investigator is responsible for ensuring the data collected are complete, accurate and recorded in a timely manner.

12.1 Submission of data

Electronic CRFs: following each participant visit the designated site staff will complete the visit specific eCRF. Once all required information is received the eCRF shall be considered complete. Project Team staff will then monitor the data for completeness and accuracy. Any eCRF discrepancies, either manual or automatic, will be addressed with the site staff for clarification.

The site Principal Investigator is responsible for ensuring the completion of accurate source documentation to support data collected on case report forms. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the trial. Source documents include, but are not limited to; participant medical records, laboratory reports, ECG tracings, X-rays, radiologist reports, participant diaries, biopsy reports, ultrasound images, participant progress notes, pharmacy records and any other reports or records of procedures performed in accordance with the protocol.

It is not acceptable for the CRF to be the only record of study participation and progress must also be recorded in each person's medical record. This is to ensure that anyone accessing the medical record has adequate knowledge that the person is a clinical trial participant.

Any document that acts as a source document (the point of the initial recording of a piece of data) should be signed and dated by the person recording or reviewing the data for issues of medical significance (for example the review of laboratory reports). Persons signing the source documents must be listed as a site staff member.

The sponsor's monitor will visit sites to conduct source document verification. The number of visits will depend upon study complexity and recruitment rate; however, the monitor will conduct a minimum of two source data verification visits during the study. These should occur shortly after enrolment of the first participant(s) and following completion of all study visits.

The Principal Investigator is responsible for retaining all essential documents listed in ICH Good Clinical Practice guidelines. These must be organised in a comprehensive filing system that is accessible to study monitors and other relevant personnel.

12.2 Linkage of data (Australian sites ONLY)

Participant data will be linked with routinely collected data from a range of population databases and registers. The collection of participant names, date of birth, sex, and post code in SHARP-C is essential for accurate data linkage. Participant data will be linked to a variety of health variables including information on hepatitis C notifications, HIV/AIDS notifications, use of hepatitis services, opioid substitution treatment, incarceration, hospitalizations, emergency department use, cancer, and mortality through the New South Wales Centre for Health Record Linkage (www.cherel.org.au) and the Australian Institute of Health and Welfare (www.aihw.gov.au). Linkage will be both retrospective and prospective, with the time period covered dependent on the properties of the specific data set. Approval from the NSW Population Health Ethics Committee and all other required Human Research Ethics Committees will be sought prior to any data linkage being performed.

Participants are given the option to opt out of the data linkage component of this study on the Participant Consent Form. Participants not wishing to have their data used in future data linkage studies may still enrol in the main study.

12.3 Archiving

The Principal Investigator is responsible for ensuring all study documents are retained for a minimum of 15 years following completion and publication of the study.

13. Ethics committee/regulatory approval and informed consent

The sponsor is responsible for ensuring regulatory approval for the study is obtained where required.

The site Principal Investigator is responsible for obtaining IRB/EC approval for the protocol and participant information and informed consent form in compliance with local regulatory requirements prior to entering any participant into the study. The approval letter/document must clearly identify the protocol and all documents approved by the IRB/IEC including version number & date of the protocol and participant information and consent form. A copy of the approval document must be sent to the study sponsor.

The site Principal Investigator must also obtain approval for any amendments to the protocol or participant information and informed consent form. The Principal Investigator must comply with all IRB/IEC reporting requirements for all adverse events, annual updates and end of study reports and must agree to abide by any IRB/IEC conditions of approval.

The site Principal Investigator (or designee) is responsible for ensuring freely-given consent is obtained from each potential participant prior to the conduct of any protocol-specific procedures. The Principal Investigator may delegate the task of obtaining consent to appropriately qualified Sub-investigator(s). Consent must be documented by the participant's dated signature on the participant information and consent form together with the dated signature of the person conducting the consent discussion.

If the participant is illiterate, an impartial witness should be present during the entire consent discussion. Once the discussion is complete, the participant must sign and date the informed consent form, if capable. The impartial witness must also sign and date the consent form along with the person who conducted the consent discussion.

A copy of the signed and dated participant information and consent form must be given to the person prior to study participation. The participant must be informed in a timely manner of any new information that becomes available during the course of the study that may affect his/her willingness to continue study participation.

This study shall be conducted in accordance with the ethical principles laid out in the Declaration of Helsinki (most current issued version) and the National Statement on Ethical Conduct in Research Involving Humans (most current issued version).

14.Confidentiality of data

14.1 Confidentiality of participant records

By signing the Clinical Trial Agreement, the site Principal Investigator agrees that the sponsor, IRB/IEC or regulatory authorities may consult and/or copy study documents to verify information in the case report form. By signing the consent form the participant agrees to these processes. The following wording may be included in the protocol.

Participant confidentiality will be maintained at all times and no documents containing the participant's name or other identifying information will be collected by the sponsor. It may be necessary for the sponsor's representatives, the IRB/IEC and regulatory authority representatives to have direct access to the participant's medical records. If study documents need to be photocopied during the process of verifying case report form data, the participant will be identified by a unique code only; full names and other identifying information will be masked.

14.2 Confidentiality of study data

By signing the Clinical Trial Agreement, the site Principal Investigator affirms to the sponsor that information provided to them by the sponsor will be maintained in confidence and divulged only as necessary to the ethics committee and institution employees directly involved in the study. Both ethics committee members and employees must also understand the confidentiality requirements for any information divulged to them. The data generated by this study will be considered confidential, except where it is included in a publication as agreed in the publication policy of this protocol.

At sites where regulations restrict the collection of full date of birth and/or initials alternative conventions may be used such as:

- Date of birth entered as 01/01/YYYY
- Initials entered as AA-AA, BB-BB, CC-CC etc.

15. Governance

The study is sponsored by UNSW and coordinated through the Kirby Institute. It is funded by the an NHMRC grant. The Kirby Institute has established governance and implementation structures which use resources efficiently to deliver program objectives on schedule.

16. Quality Control (QC) and Quality Assurance (QA)

The sponsor agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure the study is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice standards and all applicable local laws and regulations relating to the conduct of a clinical trial.

17. Publication Policy

The results of this study may be published and presented at scientific meetings. Publication of data derived from this protocol will be governed by the Protocol Steering Committee. All published data will be non-identifiable group data.

18. List of References

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19. Abbreviations List

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
DAA	Direct Acting Antiviral
ETR	End of Treatment Response, undetectable HCV RNA at the completion of treatment
FBC	Full Blood Count (haemoglobin, WCC including differentials, platelets)
HCV	Hepatitis C Virus
IEC	Institutional Ethics Committee (Human Research Ethics Committee)
INR	International Normalized Ratio
IRB	Institutional Review Board (Human Research Ethics Committee)
LFTs	Liver Function Tests – albumin, ALT, AST, alkaline phosphatase, GGT, total bilirubin, total protein
GGT	Gamma Glutamic Transpeptidase
Hgb	Haemoglobin
PWID	People Who Inject Drugs
POC	Point of Care
Reinfection	Detection of infection with an HCV strain which was distinct from the primary infecting strain among participants with either spontaneous or treatment-induced HCV virological suppression (≤15 IU/ml on Roche TaqMan).
SVR12	Sustained Virological Response, HCV RNA undetectable 12 weeks post-treatment
SVR24	Sustained Virological Response, HCV RNA undetectable 24 weeks post-treatment
WCC	White Cell Count