Strategies for hepatitis C testing and treatment in Aboriginal communities that Lead to Elimination: The SCALE-C Study

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Protocol Synopsis

Title	Strategies for hepatitis C testing and treatment in Aboriginal communities that Lead to Elimination: The SCALE-C study
Protocol registration no.	ClinicalTrials.gov Identifier: NCT03776760
Background and rationale	***Epidemiology of HCV infection in Aboriginal people*** Hepatitis C virus (HCV) infection disproportionately impacts marginalised populations, including Aboriginal and Torres Strait Islander (hereafter referred to as Aboriginal) people, people who inject drugs (PWID) and people in custodial settings. In 2015, an estimated 227,306 Australians were living with chronic HCV, of whom 22,000 were identified as Aboriginal (1), with a growing burden of HCV infection and HCV-related liver disease (2, 3). While Aboriginal people account for 2-3% of the population (4), they constitute 8-10% of all Australians living with HCV infection (1). ***Risk factors for HCV acquisition among Aboriginal people*** In Australia, an estimated 300,000 people have reported injecting an illicit drug at least once, and 90,000 reported injecting drug use (IDU) in the past year (5). The majority of existing (80%) and new (90% of 9,000 cases per annum) HCV infections are among PWID (6). Available evidence suggests that the prevalence of IDU is higher amongst the Aboriginal (3-8%) than the non-Aboriginal (1-2%) population, and has increased over recent years (7-10), in line with higher HCV prevalence and incidence among Aboriginal PWID (7, 11, 12). Furthermore, Aboriginal people account for 27% of the Australian prisoner population, with 76% having experienced repeated episodes of incarceration (13). Among Aboriginal prisoners in 2013, prevalence of chronic HCV was 31%, with higher prevalence among prisoners who were also PWID (54%) (14). Combined, this data highlights the need to implement targeted HCV testing, care and treatment, along with culturally-appropriate harm reduction strategies, for Aboriginal people. ***Improving access to HCV therapy in Australia*** Oral direct-acting antiviral (DAA) treatments have revolutionised the management of HCV infection and given rise to optimism about the potential for HCV elimination in Australia. With high cure rates (sustained virological response [SVR] >95%) after 8-12 weeks treatment, HCV DAAs provide the tools required to reverse the growing burden of liver disease and strive for HCV elimination (15). Australia is unique in providing DAA therapy to all adults living with chronic HCV, with limited restrictions. Such broad DAA access provides the opportunity to scale-up HCV treatment for Aboriginal people and affords unique opportunities to implement treatment programs in community settings. ***HCV Treatment-as-Prevention*** "Treatment-as-prevention" is a strategy used commonly in limiting spread of an infection in generalised epidemics (15). Effective HCV treatment-as-prevention requires enhanced diagnosis (to identify all people living with HCV), linkage to care and broad access to DAA therapy, alongside other harm reduction strategies. Pharmaceutical Benefits Scheme (PBS)-listed DAA therapy provides the therapeutic tools required for the implementation of an HCV treatment-as-prevention strategy. The key to HCV treatment-as-prevention effectiveness and elimination will be

	to scale up DAA implementation with equitable access and uptake to ensure no-one is left behind. ***Aboriginal Health Services*** Aboriginal Health Services (AHS) in this context meaning Aboriginal Community Controlled Health Services (ACCHS), and other Aboriginal medical services (AMS), are ideally placed to scale-up delivery of DAA therapy and ensure Aboriginal people benefit from this exciting development in HCV management. ACCHS will lead the study in each of the four study sites and will partner with relevant agencies to recruit participants for the cohort study.
Hypothesis	A community-based "test and treat" intervention integrating point-of-care HCV RNA testing, non-invasive liver disease assessment and linkage to care will lead to a reduction in HCV prevalence among people attending Aboriginal Health Services (AHS) and partnering health services, including other primary healthcare, drug treatment and harm reduction services.
Study objectives	**Primary Objective:** To evaluate the impact of a community-based "test and treat" intervention on HCV prevalence among Aboriginal people who attend participating and partnering health services. **Secondary objective(s)** • To evaluate the impact of a community-based "test and treat" intervention on HCV incidence among people attending participating and partnering health services; • To evaluate DAA treatment uptake among people with HCV infection; • To evaluate response to DAA therapy among people initiating treatment for HCV infection, and assess factors associated with failure to achieve SVR; • To evaluate DAA treatment completion and adherence among people commencing therapy; • To calculate HCV reinfection incidence, and assess factors associated with reinfection. **Exploratory objectives** • Molecular epidemiology of HCV transmission (phylogenetically reconstructed pairs/clusters of HCV sequences and factors associated with transmission in Aboriginal communities); • Attitudes and barriers to accessing HCV care and treatment among Aboriginal people and Aboriginal Medical Service staff.
Participant population	Participants will be recruited from Aboriginal health services and partnering health services. It is anticipated that approximately 600 participants will be screened for HCV infection using point-of-care testing (anti-HCV antibody and/or HCV RNA). Enrolment will continue until at least 286 people with HCV infection (HCV RNA positive) or at-risk of HCV (re)infection (HCV RNA negative) are enrolled into the SCALE-C Cohort. **Inclusion criteria** Participants must meet the following inclusion criteria to participate in the SCALE-C study: 1. Participants have voluntarily signed the informed consent form; 2. 18 years of age or older; **Exclusion criteria** 1. Pregnancy;

	2. Unable or unwilling to provide informed consent or abide by the requirements of the study. Participants with current HCV infection (HCV RNA positive) and those at risk of HCV infection (defined as injecting drug use, incarceration or receipt of opioid substation therapy within 12 months of screening) will be enrolled in the SCALE-C Cohort and followed longitudinally.
Study design	SCALE-C is an interventional cohort study recruiting people with or at risk of HCV infection from Aboriginal health services (AHS) and affiliated primary healthcare services. Participants will be screened for HCV infection using point-of-care testing (anti-HCV antibody and/or HCV RNA). Participants who test HCV positive will also be screened with rapid tests for HIV Antibody testing and Hepatitis B surface antigen. People with dual infections will be treated according to standard treatment guidelines.
Treatment of participants	Eligible participants will receive eight weeks of glecaprevir/pibrentasvir (300/120mg daily) or 12 weeks of sofosbuvir/velpatasvir (400mg/100mg) via PBS S85. Inclusion criteria for commencing DAA treatment in the simplified community-based model ("test and treat"): • Current HCV infection (HCV RNA positive) at screening/baseline or follow-up • HCV treatment naïve or treatment-experienced with interferon, pegylated-interferon, ribavirin, a first generation NS3/3a protease inhibitor (telaprevir or boceprevir), and/or sofosbuvir; • No cirrhosis or compensated cirrhosis. Exclusion criteria for DAA initiation in the simplified community-based model: • Any clinically significant co-morbid condition or contraindication to treatment with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir; • Any contraindicated medication in the product information for glecaprevir/pibrentasvir or sofosbuvir/velpatasvir; • Decompensated liver disease; • Prior DAA treatment failure; • Hepatitis B surface antigen positive; • Breastfeeding women.
Study procedures	Refer to the Schedule of Assessments.
Statistics	***Primary endpoint*****:** HCV prevalence following implementation of the community-based "test and treat" model. ***Secondary endpoints*** include: • HCV incidence; • DAA uptake: Proportion with HCV infection initiating DAA therapy; • DAA treatment outcome: Proportion who initiated DAA therapy and achieved SVR (defined as HCV RNA below the lower limit of quantitation at post treatment week 12); • DAA treatment completion; • Adherence; • Reinfection incidence post treatment. With enrolment of 286 people with or at-risk of HCV infection (estimated HCV RNA prevalence among at risk population, 35%; adjusted for 30% loss

	to follow up), the study has 90% power to detect a relative reduction in incidence of 50% from the initial to the later study period following DAA treatment scale-up (715 person years follow up).

Schedule of assessments A: Screening and follow up

Assessment / Procedure		Follow-Up Phase [a]					
Study visit	**Screening [b]**	**FU 1**	**FU 2**	**FU 3**	**FU 4**	**FU 5**	**FU 6**
Study weeks	**0**	**24**	**48**	**72**	**96**	**120**	**144**
Visit Window (Days)	**-**	**+/-30**	**+/-30**	**+/-30**	**+/-30**	**+/-30**	**+/-30**
ALL PARTICIPANTS							
Informed consent	**X**						
HCV risk assessment	**X**						
POC anti-HCV Ab +/- POC HCV RNA	**X**						
Liver fibrosis assessment: Fibroscan or APRI	**X**						
PARTICIPANTS WITH OR AT RISK OF HCV							
POC HCV RNA (Finger-stick)	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Dried blood spot collection (Finger-stick)	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Clinical assessment	**X**						
Behavioural questionnaire	**X**						
Follow-up behavioural questionnaire		**X**	**X**	**X**	**X**	**X**	**X**
Health outcomes survey (EQ-5D-5L)	**X**	**X**	**X**	**X**	**X**	**X**	**X**
POC HIV serology (HIV antibody)	**X**						
POC HBV serology (Hepatitis B surface antigen)	**X**						

Schedule of assessments B: Treatment – For participants with HCV infection

Assessment / Procedure	On and Post-Treatment Phase [a]				
Study visit	**Baseline [b]**	**Week 4**	**Week 8 [c]**	**EOT**	**PT W12**
Study weeks	**0**	**4**	**8**	**8 or 12**	**20 or 24**
Visit Window (Days)	**-**	**+/-7**	**+/-7**	**+/-7**	**+/-7**
PARTICIPANTS COMMENCING DAA TREATMENT					
POC HCV RNA (Finger-stick)	**X**			**X**	**X**
Dried blood spot collection (Finger-stick)	**X**			**X**	**X**
Clinical assessment	**X**	**X**	**X[c]**	**X**	**X**
Follow-up behavioural questionnaire				**X**	**X**
Health outcomes survey (EQ-5D-5L)				**X**	**X**
Treatment adherence		**X**	**X[c]**	**X**	
HCV genotype (Local laboratory)	**X**				
Quantitative HCV RNA (Local laboratory)	**X**				
Liver Function Tests/Full Blood Count/Biochemistry	**X**				
Pregnancy test	**X[d]**				
Study drug dispensing	**X**	**X**	**X[c]**		

Key

a On and post treatment visits can be conducted concurrently with Follow Up visits if appropriate
b Screening and baseline (treatment initiation) can (and should, if possible) occur on the same day
c For participants receiving 12 weeks sofosbuvir/velpatasvir only
d Women of child bearing potential only

1.0 Background and rationale

Epidemiology of HCV infection in Aboriginal people

HCV infection disproportionately impacts marginalised populations, including Aboriginal and Torres Strait Islander (hereafter referred to as Aboriginal) people, PWID and people in custodial settings. In 2015, an estimated 227,306 Australians were living with chronic HCV, of whom 22,000 were identified as Aboriginal (1). The burden of disease attributable to HCV among Aboriginal people is growing. Over the last five years, a staggering 43% increase in the rate of newly diagnosed HCV was documented in the Aboriginal population (117 to 167 per 100,000), compared with a 10% decrease in the non-Aboriginal population (40 to 36 per 100,000) (1).

In Australia, HCV-related morbidity and mortality have doubled in the past decade, with health care costs exceeding $220 million per year (6). Following HCV acquisition, most people develop chronic infection (75%), and are at risk of cirrhosis (7-18% at 20 years) and hepatocellular carcinoma (HCC; 1-3%) (16). Unless HCV treatment uptake is improved, the number of Australians with cirrhosis is predicted to treble to 38,130 in 2030, with an almost quadrupling in the number with liver failure and HCC (6). This is particularly concerning for the Aboriginal population. In 2012, cirrhosis and other liver diseases were the 9th leading cause of death for Aboriginal people(2), while HCC was the 2nd leading cause of cancer death, with a 3-fold higher incidence and mortality rate (3).

Risk factors for HCV acquisition among Aboriginal people

Aboriginal people are disproportionately affected by chronic and communicable disease, have higher rates of unemployment, incarceration and illicit drug use, and lower life expectancy and health literacy, compared with non-Aboriginal people (2, 4, 5, 13). Additionally, health care access is often limited and compounded by the intersectionality of racism, stigma and discrimination, especially for people living with HCV or PWID.

In Australia, an estimated 300,000 people have reported injecting an illicit drug at least once, and 90,000 reported injecting drug use (IDU) in the past year (5). The majority of existing (80%) and new (90% of 9,000 cases per annum) HCV infections are among PWID (6). Available evidence suggests that the prevalence of IDU is considerably higher amongst the Aboriginal (3-8%) than the non-Aboriginal (1-2%) population, and has increased over recent years (7-10). Among Aboriginal PWID, recent HCV prevalence estimates range between 59-70% (7, 11). HCV incidence is markedly higher in Aboriginal PWID (31 per 100 py, 95% CI 19, 50) than in the general PWID population (11 per 100 py, 95% CI 9, 14) (12). Compared with non-Aboriginal PWID, Aboriginal PWID are more likely to start injecting at an early age, report receptive needle sharing, inject more frequently and in public and have a history of incarceration (7, 9, 12, 17).

Furthermore, Aboriginal people account for 27% of the Australian prisoner population, with 76% having experienced repeated episodes of incarceration (13). Among Aboriginal prisoners in 2013, prevalence of chronic HCV was 31%, with higher prevalence among prisoners who were also PWID (54%) (14). Combined, this data highlights the need to implement targeted HCV testing, care and treatment, along with culturally-appropriate harm reduction strategies, for Aboriginal people.

Improving access to HCV therapy in Australia

Oral direct-acting antiviral (DAA) treatments have revolutionised the management of HCV infection and given rise to optimism about the potential for HCV elimination in Australia. However, marginalised populations often fare less well in relation to access to health care innovations, and this is particularly the case for Aboriginal people. In this context, it cannot be guaranteed that the roll out of new HCV treatments will have equal impact for Aboriginal people. Understanding how HCV treatment is accessed by Aboriginal people is essential to avoid creating further gaps in liver disease and Aboriginal health outcomes.

With high cure rates (>95%) after 8-12 weeks treatment, HCV DAAs provide the tools required to reverse the growing burden of liver disease and strive for HCV elimination (15). On March 1st 2016, HCV DAA treatments were listed on the Pharmaceutical Benefits Scheme (PBS). Australia is unique in providing DAA therapy to all adults living with chronic HCV, with no liver disease, drug and alcohol use, or prescriber restrictions. Between March–December 2016, more than 30,000 Australians commenced DAA treatment (18, 19). Such broad DAA access provides the opportunity to scale-up HCV treatment for Aboriginal people and affords unique opportunities to implement treatment programs in community settings.

HCV Treatment-as-Prevention

One of the goals of the United Nations 2030 Agenda for Sustainable Development is the elimination of viral hepatitis as a public health threat. To achieve HCV elimination in Australia, populations with high seroprevalence will require targeted interventions. While Aboriginal people account for 2-3% of the population (4), they constitute 8-10% of all Australians living with chronic HCV (1). Reducing HCV incidence and increasing access to HCV therapy are priorities of national and jurisdictional Hepatitis C strategies (20, 21), all of which highlight Aboriginal people as a priority population, given the significant burden of disease (1), rising HCV incidence (1) and historically low rates of treatment uptake (21).

"Treatment-as-prevention", currently used in the context of HIV, incorporates treatment as a tool for limiting spread of an infection in generalised epidemics (15). Modelling indicates that substantial reductions in HCV incidence and prevalence could be achieved by targeted DAA treatment scale-up amongst those at highest risk of ongoing transmission (15). Effective HCV treatment-as-prevention requires enhanced diagnosis (to identify all people living with HCV), linkage to care and broad access to DAA therapy, along with harm reduction strategies. PBS-listed DAA therapy provides the therapeutic tools required for the

implementation of an HCV treatment-as-prevention strategy, making Australia a global leader in addressing the public health impact of HCV infection. The key to HCV treatment-as-prevention effectiveness and elimination will be sustained DAA scale-up with equitable access and uptake in high-risk populations, including Aboriginal people, to ensure no-one is left behind.

Aboriginal health services

Aboriginal Health Services are ideally placed to deliver DAA therapy and ensure Aboriginal people benefit from this exciting development in HCV management. They often see more than 50% of the resident Aboriginal and Torres Strait Islander population and have strong partnerships with other services locally such as harm reduction and alcohol and other drug services.

2.0 Study objectives

2.1 Hypothesis

A community-based "test and treat" intervention integrating point-of-care HCV RNA testing, non-invasive liver disease assessment and linkage to care will lead to a reduction in HCV prevalence among people attending AHS and partnering health services.

2.2 Primary objective

To evaluate the impact of a community-based "test and treat" intervention on HCV prevalence among people attending AHS and partnering services.

2.3 Secondary objective(s)

- To evaluate the impact of a community-based "test and treat" intervention on HCV incidence among people attending AHS;
- To evaluate DAA treatment uptake among people with HCV infection;
- To evaluate response to DAA therapy among people initiating treatment for HCV infection, and assess factors associated with failure to achieve SVR;
- To evaluate the proportion of participants who complete treatment;
- To evaluate treatment adherence among those who commence DAA therapy;
- To calculate HCV reinfection incidence, and assess factors associated with reinfection.

2.4 Exploratory objectives

- Molecular epidemiology of HCV transmission among Aboriginal people (phylogenetically reconstructed pairs/clusters of HCV sequences and factors associated with transmission;
- Attitudes and barriers to accessing HCV care and treatment among Aboriginal people and AHS staff

3.0 Participant population

3.1 Number of Participants

Participants will be recruited from AHS and partnering affiliated health services. It is anticipated that approximately 600 participants will be screened for HCV infection using point-of-care testing, assuming that 50% of screened participants are AHS clients (HCV RNA prevalence 5%, n=15; at risk 5%, n=15) and 50% are clients of affiliated drug treatment and harm reduction services (HCV RNA prevalence 35%, n=105; at risk 65%, n=195). Enrolment will continue until at least 286 people with HCV infection (HCV RNA positive) or at risk of HCV (re)infection (HCV RNA negative) are enrolled.

3.2 Participant Selection Criteria

	Inclusion	Exclusion
SCALE-C Screening	1. 18 years of age or older; 2. Signed informed consent form.	1. Pregnancy
SCALE-C Cohort	1. HCV RNA positive at screening; OR 2. At risk of HCV infection *Defined as a person who, in the last 12 months, has:* a. injected drugs, b. been incarcerated, and/or c. received opioid substitution therapy.	
"Test and treat": Community-based DAA treatment	1. HCV RNA positive at screening OR follow up; 2. HCV treatment naïve or treatment-experienced with interferon, pegylated-interferon, ribavirin, a first generation NS3/3a protease inhibitor (telaprevir or boceprevir), and/or sofosbuvir; 3. No cirrhosis or compensated cirrhosis. Participants with HCV reinfection following DAA-based treatment are eligible.	1. Clinically significant co-morbid condition or contraindication to treatment with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir; 2. Any contraindicated medication in the product information for glecaprevir/pibrentasvir or sofosbuvir/velpatasvir; 3. Decompensated liver disease; 4. Hepatitis B surface antigen positive; 5. Breastfeeding women; 6. Prior DAA treatment failure; a. Defined as on-treatment failure (virological non-response or breakthrough) or post-treatment relapse b. Participants who have failed prior HCV treatment with a regimen containing an NS5A inhibitor (including, but not limited to, elbasvir, ledipasvir, ombitasvir, velpatasvir) and/or a second generation NS3/4a protease inhibitor (including, but not limited to, grazoprevir, paritaprevir, pibrentasvir, voxilaprevir) are *ineligible.*

4. Study design

4.1 Summary of study design

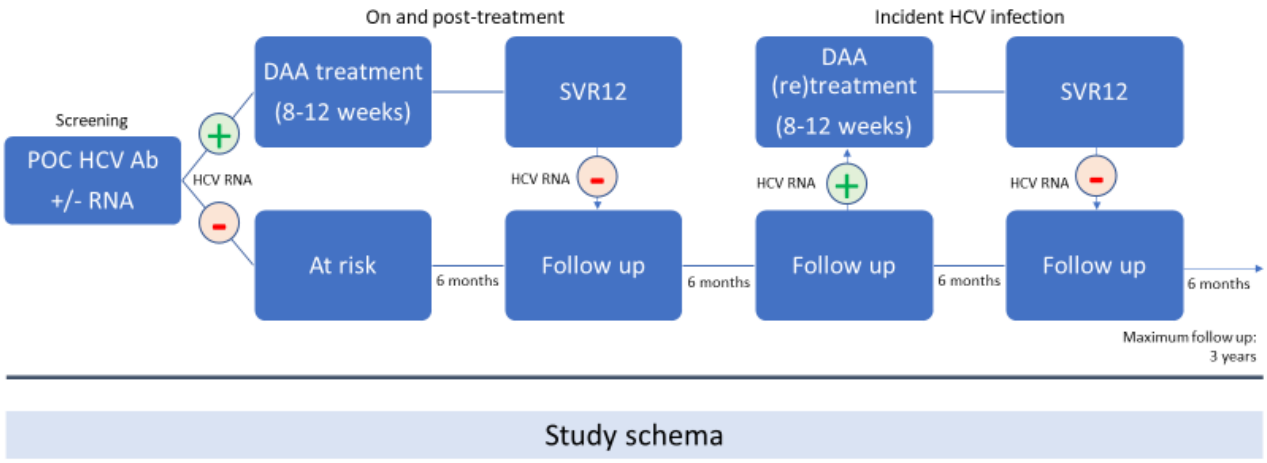

Figure 1. SCALE-C study schema

This study will be conducted as an interventional cohort study. A total of 286 people with or at risk of HCV infection will be enrolled from AHS and partnering health services. Individuals at risk of HCV infection are defined by self-reported injecting drug use, incarceration or receipt of opioid substitution therapy within 12 months of screening.

Participants will receive a community-based "test and treat" intervention integrating point-of-care HCV testing, non-invasive liver fibrosis assessment (Fibroscan or APRI) and linkage to care as a strategy to increase HCV diagnosis and testing, enhance scale-up of DAA therapy and reduce HCV prevalence and incidence (Figure 1).

The "test and treat" intervention will consist of:

- Point-of-care HCV testing (anti-HCV Ab or HCV RNA)
    - Choice of initial test will be based on a short HCV risk assessment at enrolment (Figure 2)
- Non-invasive liver fibrosis assessment (Fibroscan® or APRI)
- Linkage to care (with medical or nursing assessment), including education regarding HCV transmission and harm reduction
- Immediate DAA initiation (if indicated and clinically appropriate)

Recruitment into the SCALE-C cohort will remain open throughout the study period. Enrolment may occur in concert with standard of care healthcare provision (following written informed consent).

To enhance recruitment and follow up targeted periods of recruitment will be developed in partnership with the participating AHS. Models of recruitment will be provided to AHS for consideration to drive recruitment. Ultimately AHS will determine appropriate models of recruitment to match their target population.

The study consists of screening, HCV treatment (8-12 weeks) if appropriate, and follow-up (up to three years post enrolment). Treated participants will transition into the HCV RNA negative at-risk cohort to assess for incident infection (reinfection) after viral cure (SVR12).

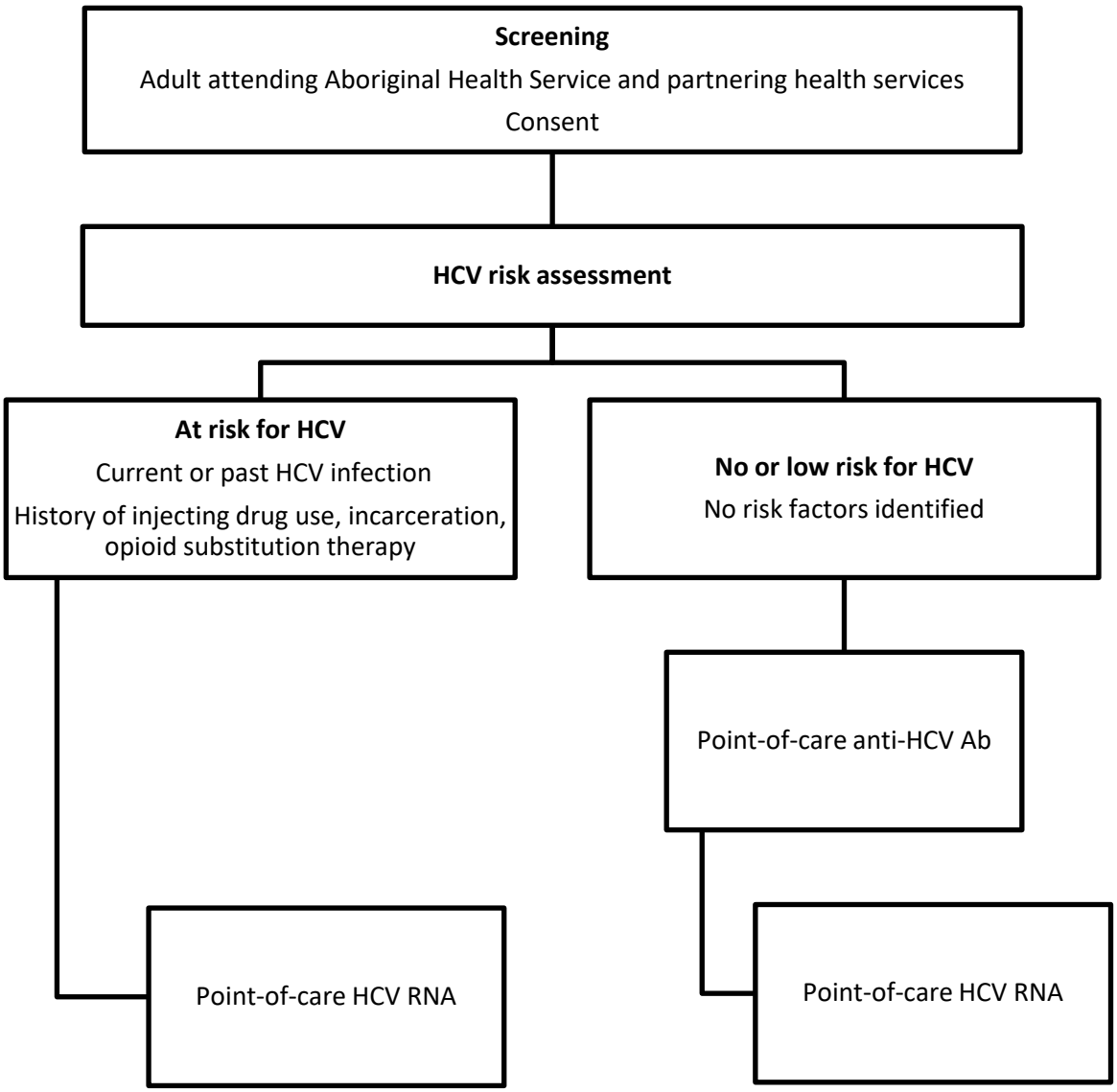

Figure 2. HCV risk assessment at screening and testing pathway

4.2 Visit Schedule

All participants will complete a screening visit as outlined below and in the Schedule of Assessments.

Those participants who are HCV RNA positive will be offered DAA therapy. Participants who decide to initiate DAA treatment will have on-treatment and post-treatment assessments as outlined in the Schedule of Assessments and described in Section 6.0. The treatment regimen of eight weeks glecaprevir/pibrentasvir or 12 weeks sofosbuvir/velpatasvir will be prescribed via the PBS S85. Participants who are HCV RNA positive may commence DAA treatment at any time during the study.

Following enrolment into the SCALE-C Cohort, regardless of HCV RNA or DAA treatment initiation, a follow-up visit will be conducted every 6 months for the duration of the study (up to three years; FU1–FU6).

4.3 Treatment Discontinuation Criteria

Participants may discontinue treatment for reasons including, but not limited to, the following:

- Adverse events (AEs) or laboratory abnormalities for which treatment discontinuation is deemed necessary by the treating clinician.
- Significant protocol violation.
- Participant request to discontinue study drug or withdraw from the study for any reason.
- Discontinuation of the study by the Kirby Institute, regulatory agencies or a Human Research Ethics Committee / Research Ethics Committee / Institutional Review Board.

Participants who cease treatment will, wherever possible, continue to be followed up according to the protocol study plan by completing the end of treatment (EOT) visit at the time of treatment termination, post-treatment week 12 for treatment outcome, and if applicable, long term follow up for reinfection or retreatment.

Participants may revoke consent without jeopardizing their relationship with either their doctor, the AHS, UNSW Sydney, or SAHMRI. If a participant wishes to withdraw from the study then, if possible, all assessments scheduled for the post-treatment week 12 visit should be completed.

5. Treatment of participants

Eligible participants will receive eight weeks of glecaprevir/pibrentasvir 300/120 mg daily or 12 weeks of sofosbuvir/velpatasvir 400mg/100mg once daily via PBS S85. Choice of DAA pan-genotypic DAA regimen is at the discretion of the treating physician.

*For participants to be eligible to receive **eight weeks of glecaprevir/pibrentasvir**, they must meet the following criteria:*

1. HCV infection (HCV RNA positive)
2. HCV treatment naïve
3. Absence of cirrhosis
    a. Absence of cirrhosis is defined as liver stiffness measurement <12.5kPa (Fibroscan) or APRI <1.0.

*For participants to be eligible to receive **12 weeks of sofosbuvir/velpatasvir**, they must meet the following criteria:*

1. HCV infection (HCV RNA positive)
2. HCV treatment naïve or HCV treatment experienced
3. Absence of cirrhosis or compensated cirrhosis
    a. Absence of cirrhosis is defined as liver stiffness measurement <12.5kPa (Fibroscan) or APRI <1.0.
    b. Compensated cirrhosis is defined as Child-Turcotte-Pugh Class A (score 5-6) with absence of complications related to hepatic insufficiency (jaundice or hepatic encephalopathy) or portal hypertension (ascites or variceal haemorrhage).

Participants with HIV/HCV co-infection are suitable for the "test and treat" model at the discretion of the site investigator following review of drug-drug interactions.

Participants with HBV/HCV co-infection (Hepatitis B surface antigen positive) are excluded from the "test and treat" model, but may be followed longitudinally in the SCALE-C cohort. This is for participant safety, as people with HCV/HBV co-infection need to be assessed and considered for concurrent HBV nucleos(t)ide analogue therapy while receiving HCV DAA therapy, and require more frequent on-treatment monitoring.

Participants with cirrhosis are recommended to have screening liver ultrasound for hepatocellular carcinoma.

Participants with decompensated cirrhosis or prior DAA treatment failure (as defined in the exclusion criteria above) are excluded from the simplified community-based treatment model. These participants should be discussed with and/or referred to a specialist. These participants can be enrolled and followed longitudinally in the SCALE-C cohort.

5.1 Treatment Adherence

Treatment will be administered in four-weekly supply as per the PBS. The time and date of first study dose will be recorded. Treatment adherence will be monitored by self-report.

5.2 Prior and Concomitant Medications

The use of concomitant medications prior to, during, and post-treatment must be in line with the product information for glecaprevir/pibrentasvir or sofosbuvir/velpatasvir. The treating clinician should thoroughly review the participants medical history and review all medications the patient is taking prior to treatment and commences taking during treatment for potential drug-drug interactions (https://www.hep-druginteractions.org/).

6. Study procedures

6.1 Visits and Procedures

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

Anti-HCV Ab (POC)	SD Bioline HCV point-of-care assay
APRI	AST to platelet ratio
HCV RNA (POC)	Xpert® HCV Viral Load Fingerstick point-of-care assay
DBS	Dried Blood Spot research sample collection
Behavioural questionnaire	Behavioural survey (screening or follow-up version as applicable)
Health outcomes survey	EQ-5D-5L
Treatment adherence	Adherence questionnaire
HCV RNA (SOC) [a]	Quantitative HCV RNA via local laboratory (baseline only)
HCV genotype (SOC) [a]	HCV genotype via local laboratory (baseline only)
Liver function tests [a]	ALT, AST, GGT, total bilirubin, albumin, alkaline phosphatase (baseline only)
Biochemistry [a]	Creatinine, sodium, chloride, potassium (baseline only)
Full blood count [a]	Haemoglobin, white blood cells, platelets, neutrophils (baseline only)
HIV serology (POC)	HIV Ab (screening only)
HBV serology (POC)	Hepatitis B surface antigen (HepBsAg) (screening only)
FibroScan®	Transient elastography
Pregnancy test	For women of childbearing potential, a negative urine (or serum) βHCG test at baseline

[a] Only when clinically indicated

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

Screening visit (All participants)

- Informed consent
- HCV risk assessment (Figure 2)
    - ***Reported risk for HCV infection***
        i. Known current or past HCV infection (self-report)
        ii. Risk behaviour for HCV transmission: History of injecting drug use, history of incarceration, receipt of opioid substitution therapy (self-report)
    - ***No reported risk for HCV infection***
- Point-of-care HCV testing
    - Point-of-care anti-HCV antibody (***no reported risk for HCV infection***)

      AND/OR
    - Point-of-care HCV RNA (***reported risk for HCV infection or positive point-of-care anti-HCV Ab***)
- Non-invasive liver disease assessment (Fibroscan® or APRI)
    - Fibroscan® will be performed in preference to APRI if available.

Participants will be notified of their point-of-care anti-HCV Ab and/or HCV RNA results on the same-day (where possible).

Participants who are anti-HCV Ab negative and report no risk factors for HCV acquisition will complete the above screening procedures but will not be followed longitudinally.

Participants with ***current HCV infection*** (HCV RNA positive) and/or participants who report being ***at risk of HCV infection*** (HCV RNA negative; history of injecting drug use, history of incarceration, receipt of opioid substitution therapy with 12 months of screening) will undergo the following assessments:

- Point-of-care HCV RNA (if not performed previously)
- Point-of-care HIV and HBV serology
- Collection of dried blood spot (DBS) sample (research sample)
- Screening behavioural questionnaire
- Health outcomes survey (EQ-5D-5L)
- Education regarding HCV transmission and risk reduction

Baseline visit (Point-of-care HCV RNA positive participants only)

Assessment for DAA initiation

This can, and should (if possible), be conducted on the day of the screening (or follow up) visit.

- Clinical assessment with a study nurse

  If clinically indicated, the following standard-of-care blood tests will be collected:
  - Phlebotomy for liver function tests, full blood count, biochemistry
  - HCV genotyping via local laboratory
  - HCV RNA (quantitative or qualitative) via local laboratory
- Pregnancy test (for women of childbearing potential only)
- Initiation of pan-genotypic DAA therapy (glecaprevir/pibrentasvir or sofosbuvir/velpatasvir) following discussion with an experienced clinician (face-to-face or remote), if appropriate

Point-of-care HCV RNA positive participants assessed as suitable and willing for treatment will be prescribed eight weeks glevaprevir/pibrentasvir or 12 weeks sofosbuvir/velpatasvir under PBS S85 (dispensed as a 4-week supply). The time of the first dose of therapy will be recorded.

Participants not deemed suitable for treatment under this simplified community-based model of care will be referred for specialist follow-up.

For point-of-care HCV RNA positive participants who decline DAA treatment, site study staff will discuss with the participant the reasons for not initiating DAA treatment. These participants may remain in the cohort and will be followed longitudinally. They will also be approached for involvement in the qualitative study.

On-Treatment and Post-Treatment Phase (For participants who initiate DAA treatment)

On-Treatment Week 4 and Week 8

The following procedures will occur at Week 4 and Week 8 on-treatment:

- Clinical assessment with nurse (as required)
    - Clinical assessment will be conducted on an as-needed basis at discretion of the participant and/or the nurse.
- Participants will receive a 4-week supply of DAA therapy (glecaprevir/pibrenatasvir or sofosbuvir/velpatasvir), as appropriate
- Treatment adherence questionnaire

End of Treatment (EOT)

Participants will return at end of treatment for the following:

- Clinical assessment with nurse
- POC HCV RNA
- DBS (research sample collection)
- Treatment adherence questionnaire
- Follow-up behavioural questionnaire
- Health outcomes survey (EQ-5D-5L)

Post-treatment week 12 (PTW12)

Participants will return 12-weeks post EOT for the following:

- Clinical assessment with a nurse
- POC HCV RNA
- DBS (research sample collection)
- Follow-up behavioural questionnaire
- Health outcomes survey (EQ-5D-5L)

Follow Up Phase (All participants)

Follow up 1, 2, 3, 4, 5, 6

Participants with or at risk of HCV infection will return every 6 months enrolment for the following:

- POC HCV RNA
- DBS (research sample collection)
- Follow-up behavioural questionnaire
- Health outcomes survey (EQ-5D-5L)

Unscheduled visits

Unscheduled visits may occur for reasons including, but not limited to, adverse events, early treatment discontinuation or study termination. In the event of treatment or study termination an unscheduled visit should be performed where possible.

6.2 Study Questionnaires

All participants will complete a behavioural questionnaire, health outcomes survey (EQ-5D-5L) and treatment adherence questionnaire at selected study visits as described below.

Behavioural Questionnaire

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

- Demographics
- HIV and drug treatment history
- Drug and alcohol usage
- Injecting risk behaviors

An abbreviated behavioural questionnaire (follow-up) will be administered at EOT, PTW12 and FU1-6.

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.

Adherence Survey

Adherence to glecaprevir/pibrentasvir or sofosbuvir/velpatasvir will be assessed by a four-weekly structured self-report adherence questionnaire.

7. Adverse Events (AEs) and Product Complaints

7.1.1 Adverse Event definition

The medications for this study are supplied via the PBS. Adverse Events and adverse drug reactions will be reported to the Therapeutic Goods Administration as per standard practice for PBS prescribed medications.

7.1.2 Serious Adverse Event (SAE) (including Serious Adverse Drug Reactions)

The medications for this study are supplied via the PBS. Serious Adverse Drug Reactions will be reported to the Therapeutic Goods Administration as per standard practice for PBS prescribed medications.

8. Packaging, labelling, storage and accountability of treatment

The medications for this study are supplied via the PBS. The packaging, labelling and accountability of prescribed treatment will be as per PBS guidelines.

9. Biological samples

9.1 Laboratory supplies and sample processing

Laboratory supplies for collection of research specimens (DBS) will be supplied by the Kirby Institute.

A DBS sample will be collected at the time points specified in the Schedule of Assessments. Samples will be collected by sites, dried (4 hours minimum but preferably overnight) and then posted to the Kirby Institute laboratory within 1 week of collection for storage at -80°C.

DBS samples will be used for study endpoint analysis. HCV RNA 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, to examine the prevalence of mixed infection, to look at clusters and networks in communities and factors associated with relapse including resistance-associated substitutions (RAS) and to perform phylogenetic analyses to examine molecular epidemiology. For HCV phylogenetic analysis, only viral RNA is extracted, amplified and sequenced. No human genomic analysis is being proposed. There is no potential to identify human genetic traits.

9.2 Shipping of biological samples

DBS samples must be posted to the Kirby Institute laboratory once dried (4 hours minimum, but preferably overnight). Each DBS sample card is sealed in a foil zip lock bag which is then sealed in a clear zip lock bag. Samples are posted within 1 week of collection via Express Post.

9.3 HCV RNA Point of Care Testing

A GenExpert machine will be placed within the AHS as part of the study. QA and training will be provided by the KI team. As specified in the Schedule of Assessments, HCV RNA detection will be performed using the Xpert® HCV Viral Load Fingerstick point-of-care assay with finger-stick whole-blood samples, as previously validated by our

group (22). A whole-blood sample will be collected from participants via a finger-stick and collected into a 100 µL minivette collection tube. Immediately after collection, 100 µL of capillary whole blood will be placed directly into the Xpert® HCV Viral Load Fingerstick cartridge (Cepheid, USA; lower limit of quantification of 10 IU/mL) for on-site HCV RNA testing. HCV Viral Load testing of capillary whole blood will be done on a clinic-based GeneXpert R2 6-colour, two module machine operated by a trained nurse as per the manufacturer's instructions. The time to result for this assay is 60 minutes.

9.4 Anti-HCV antibody Point of Care Testing

As specified in the Schedule of Assessment, qualitative anti-HCV antibody testing will be performed using the Alere SD Bioline HCV – a rapid 5-20 minute point-of-care qualitative immunoassay for detection of anti-HCV antibody. A 10 µL whole blood sample will be collected from participants via a finger stick and added to the round specimen well followed by four drops of the assay diluent. The device provides a visual indicator of the results to display positive, negative or invalid results. As determined by the prescribing physician, point-of-care testing results may be repeated/confirmed with standard laboratory immunoassays via venepuncture.

9.5 HIV 1/2 Antibody Point of Care Testing

At study enrolment, qualitative HIV antibody testing will be performed using the Alere™ HIV Combo: a point-of-care, 20-minute immunoassay for the qualitative detection HIV-1 p24 antigen (Ag) and antibodies (Ab) to HIV-1 and HIV-2. A 50 µL capillary (whole blood) sample will be collected from the participant and applied to the Sample Pad followed by a Chase Buffer. The device provides a visual indicator of the results to display positive, negative or invalid results. As determined by the prescribing clinician, point-of-care testing results may be repeated/confirmed with standard laboratory immunoassays via venepuncture.

This test is approved by the Australian Government Therapeutic Goods Administration (TGA) and registered as a Medical Device – IVD Class 4 by Inverness Medical Innovations Australia Pty Ltd T/A Alere (Queensland, Australia) and manufactured by Alere Medical Co Ltd (Chiba-ken, Japan).

9.6 HBV Surface Antigen Point of Care Testing

At study enrolment, qualitative hepatitis B surface antigen testing will be performed using the Alere Determine ™ HBsAg – a rapid 15-minute point-of-care in-vitro qualitative immunoassay for detection of hepatitis B surface antigen. A 50 µL whole blood sample will be collected from participants via a finger stick and added to the Alere Determine test pad with the Alere Determine ™ Chase Buffer (Chase Buffer prepared in phosphate buffer). The device provides a visual indicator of the results to display positive, negative or invalid results. As determined by the prescribing physician, point-of-care testing results may be repeated/confirmed with standard laboratory immunoassays via venepuncture.

This test is currently not approved by the TGA.

9.7 HCV RNA Recurrence

Among people with an end of treatment response, participants with HCV RNA recurrence (detectable HCV RNA) will be identified. HCV sequencing will be performed from dried blood samples using Core-E2, NS5A or NS5B Sanger sequencing (23). HCV reinfection will be defined by the detection of infection with a strain distinct from the primary infecting strain based on defined genetic distance-based cut-offs and phylogenetic tree construction for reinfection and relapse developed by the investigators (23).

9.8 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. Additional consent will be sought for permission to store any remaining DBS samples after sample analyses for study endpoints for future hepatitis C related research. As part of the informed consent process and form, participants will indicate their choice using tick boxes to the storage of remaining samples for use in hepatitis C related future research. Samples from participants who indicate they do not wish for their samples to be used in future research, will be destroyed, or returned to participates if indicated, following sample analyses for study endpoints

10. Statistics

Statistical Analyses and Sample Size Calculations

***Primary endpoint*:** The primary endpoint for the HCV treatment as prevention evaluation is HCV prevalence following implementation of the community-based "test and treat" model.

Secondary endpoints include:

- HCV incidence;
- DAA uptake: Proportion with HCV infection initiating DAA therapy;
- DAA treatment outcome: Proportion who initiated DAA therapy and achieved SVR (defined as HCV RNA below the lower limit of quantitation at post treatment week 12);
- DAA treatment completion: Proportion who completed prescribed treatment course;
- Adherence;
- Reinfection incidence post treatment.

The impact of rapid DAA treatment scale-up on HCV incidence and prevalence

Hypothesis: Rapid DAA scale-up will reduce HCV prevalence by >50%

Outcome: Prevalence of HCV infection

Statistical analysis: The proportion of people with current HCV infection (HCV RNA positive) will be calculated by study period. Confidence intervals for proportions will be calculated.

Sample Size: With enrolment of 370 participants (estimated HCV RNA prevalence in Year One, 35%; alpha=0.05; loss to follow up, 30%), the study has 90% power to detect a relative reduction in HCV RNA prevalence of 50% from the initial to the later study period following scale-up of testing and treatment.

Hypothesis: Rapid DAA scale-up will reduce HCV incidence by >50%

Outcome: Incidence of HCV infection

Statistical analysis: HCV incidence will be calculated using person-time of observation. The estimated date of infection will be calculated as the midpoint between the dates of the last undetectable HCV RNA test (or end of treatment) and the first detectable HCV RNA test at the time of HCV infection. Time at risk will commence at the date of first undetectable HCV RNA (or end of treatment), and end at the estimated date of infection, death, loss-to-follow up or end of study. Confidence intervals for rates will be calculated using a Poisson distribution. Poisson regression analysis (or another time-to-event analysis) will be used to estimate crude and adjusted incidence rate ratios (IRR) and corresponding 95% CI to evaluate factors associated with incident infection.

Uptake of DAA therapy among people with HCV infection attending Aboriginal Medical Services

Hypothesis: A community-based "test and treat" intervention integrating point-of-care HCV testing will lead to increased HCV treatment uptake among people attending Aboriginal Medical Services.

Outcome: Treatment uptake (proportion of individuals with HCV infection [HCV RNA positive] initiating DAA therapy)

Statistical analysis: Among people with HCV infection, the proportion of people who initiate DAA therapy will be calculated. Factors associated with DAA uptake will be assessed by logistic regression analyses.

Sample Size: Given the assumed population distribution, we will enrol 120 participants with prevalent chronic HCV infection and 29 with incident HCV infection (with spontaneous clearance in 25% of incident cases). As such, 142 will be considered for DAA therapy. Assuming DAA uptake of 70% (based on LiveRLife [unpublished data]), the 95% CI around this estimate is 62-78%. We will have 80% power to detect an odds ratio of 2.66 or greater (alpha=0.05) for a variable that is 50% prevalent (i.e. recent injecting drug use).

Response to DAA therapy among people with chronic HCV infection

Hypothesis: A community-based "test and treat" intervention integrating point-of-care HCV testing among people attending Aboriginal Medical Services will lead to HCV treatment response of ≥90%.

Outcome: Treatment response (SVR, defined as HCV RNA below the lower limit of quantitation 12 weeks following end of treatment).

Statistical analysis: The proportion of people achieving SVR12 will be calculated with corresponding 95% CI. Factors associated with treatment response will be assessed by logistic regression analyses.

The proportion completing the prescribed treatment course will be calculated with corresponding 95%CI. Factors associated with treatment completion will be assess by logistic regression analysis.

Estimate incidence of HCV reinfection after successful DAA therapy

Hypothesis: HCV reinfection following treatment will be associated with ongoing high-risk behaviours facilitating transmission.

Outcome: Incidence of HCV reinfection following DAA therapy

Statistical analysis: Rates of HCV reinfection following treatment will be calculated using person-time of observation, with the methodology described in Aim 1, except that time at risk will commence at the date of end of treatment. Poisson regression analysis (or another time-to-event analysis) will be used to estimate crude and adjusted IRRs and corresponding 95% CI to evaluate factors associated with reinfection.

11. Data Safety and Monitoring Board (DSMB)

A Data Safety Monitoring Board will not be used for this study as treatment is being prescribed and supplied according to PBS indications.

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 Data Linkage

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 postcode in SCALE-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 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), SA-NT DataLink (https://www.santdatalink.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.

12.2 Submission of data

Electronic CRFs: following each participant visit the designated site staff will complete the visit specific eCRF. Once a copy of the required information is received the eCRF shall be considered complete. Project Team staff will then review and 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.

The sponsor's monitor may visit sites to conduct source document verification. The number of visits will depend upon study complexity and recruitment rate; however, the monitor will conduct source data verification visits during the study as required.

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.

12.3 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.

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/EC including version number and 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/EC reporting requirements for all annual updates and end of study reports and must agree to abide by any IRB/EC 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) or

nurse(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.

A copy of the signed and dated participant information and consent form must be given to the person prior to study participation. The participant or their legally authorised representative 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/EC 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.

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/EC 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, the following conventions will be used:

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

15. Governance

Aboriginal community governance committee- comprising site representatives and KI and SAHMRI staff will coordinate all aspect of the study. This research protocol is sponsored by SAHMRI and UNSW Sydney. The study is coordinated through the Kirby Institute for Infection and Immunity in Society, UNSW Sydney and SAHMRI. The NHMRC grant is administered through Flinders University in South Australia. The Kirby Institute and SAHMRI have established governance and implementation structures which use resources efficiently to deliver program objectives on schedule.

Coordinating investigators involved in the study include Associate Professor James Ward (SAHMRI, Flinders University), Dr Marianne Martinello (Kirby Institute, UNSW Sydney), Associate Professor Jason Grebely (Kirby Institute, UNSW Sydney), Associate Professor Gail Matthews (Kirby Institute, UNSW Sydney), Professor Mark Boyd (The University of Adelaide), D Tanya Applegate (Kirby Institute, UNSW Sydney), Professor Carla Treloar (Centre for Health and Social Research, UNSW Sydney), and Associate Professor Kathy Petoumenos (Kirby Institute, UNSW Sydney).

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 grouped data and will follow the guidelines set forth by the International Committee of Medical Journal Editors (ICMJE).

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19. Abbreviations List

AE	Adverse Event
ALT	Alanine Aminotransferase
APRI	AST to Platelet Ratio Index
AST	Aspartate Aminotransferase
CI	Confidence interval
DAA	Direct Acting Antiviral
DBS	Dried Blood Spot
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Form
ETR	End of Treatment
HCV	Hepatitis C Virus
IFN	Interferon
IRR	Incidence Rate Ratio
NSP	Needle Syringe Program
OR	Odds Ratio
PBS	Pharmaceutical Benefits Scheme
POC	Point-of-Care
PWID	People Who Inject Drugs
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAHMRI	South Australian Health and Medical Research Institute
SOC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR12	Sustained Virological Response (HCV RNA below the lower limit of quantitation at 12 weeks post-treatment)
UNSW	University of New South Wales

Appendix 1: Examples of other studies

HCV testing, diagnosis and assessment of HCV-related liver disease – the LiveRLife Project

On-site HCV testing with integrated care improves linkage to HCV care and treatment among PWID (24). In 2014-2017, the LiveRLife project piloted an intervention using a liver health promotion campaign, non-invasive liver fibrosis assessment (transient elastrography; Fibroscan®), dried-blood spot testing, and point-of-care HCV RNA testing (GeneXpert, Cepheid) among PWID attending 13 sites in NSW, Queensland, and South Australia (seven drug treatment clinics, one Aboriginal community-based primary health clinic, the Sydney Medically Supervised Injecting Centre, one homelessness service, and one needle and syringe program site) (25).

This project:

- Evaluated knowledge/attitudes about liver disease and used social marketing methods to develop evidence-based messaging to enhance liver disease assessment;
- Developed LiveRLife resources through extensive focus group testing (posters, 16-page educational booklet, Fibroscan® results card, LiveRLife website, and educational film);
- Established a cohort study of PWID. Each clinic had four campaign days over four weeks. Participants completed a survey, Fibroscan® assessment, nurse assessment and finger-stick HCV RNA testing, with 60% returning for clinical follow-up 2-12 weeks post-intervention (26);
- Performed the first international evaluation of point-of-care finger-stick HCV RNA test (27, 28).

Among Aboriginal people enrolled, the majority reported a history of IDU (ever 97%, current 75%) and incarceration (75%), and HCV RNA prevalence was 45%, with prior anti-HCV Ab antibody and HCV RNA testing were reported by 64% and 60%, respectively (unpublished data). There was high acceptability (87%) of transient elastography. Of note, among those with detectable HCV RNA, 74% were willing to commence HCV treatment. These data support use of this model in a larger prospective study to evaluate whether this intervention can increase HCV testing, access to care and treatment, and reduce risk behaviours associated with transmission among Aboriginal people attending culturally-appropriate community primary healthcare facilities.