STOPC

Surveillance and Treatment of Prisoners with Hepatitis C

A study to assess the feasibility of HCV treatment as prevention with interferon-free Direct Acting Antivirals (DAAs) in the prison setting

Protocol number: **VHCRP1302**

Protocol version: **7.0**

Protocol date: **25 Jun 2019**

Name of sponsor: University of New South Wales

Title and name of Coordinating Principal Investigator (CPI):
Professor Gregory J Dore and Professor Andrew Lloyd

Table of contents

Protocol Synopsis

Title	Surveillance and Treatment of Prisoners with Hepatitis C (SToP-C) A study to assess the feasibility of HCV treatment as prevention with interferon-free Direct Acting Antivirals (DAAs) in the prison setting
Background and rationale	The global burden of hepatitis C virus (HCV) infection continues to rise. People who inject drugs (PWID) represent the core of the HCV epidemic in developed countries, accounting for the majority of new (80%) and existing (60%) cases. Among many populations of PWID, high HCV incidence and prevalence are observed. Although harm reduction strategies such as needle syringe programs (NSP) and opiate substitution treatment (OST) have been successful for HIV, these strategies have limited evidence for HCV prevention and often require a combination of strategies to be successful. HCV-related morbidity and mortality also continues to rise. The natural history of chronic HCV (cirrhosis risk escalates after 15-20 years) and ageing cohorts in many countries means that a large burden of advanced liver disease is anticipated in the next decade, particularly among older former and current PWID. Although HCV treatment for PWID has been demonstrated to be safe and effective, treatment uptake remains low. HCV treatment with interferon-free DAA regimens is both curative and circumscribed in duration (generally 12 weeks) – two key features which hold great promise for the potential effectiveness of HCV treatment as prevention. Over the next 1-2 years, simple (once-daily), tolerable, short-duration (12-24 weeks) therapy with interferon-free DAA regimens with extremely high efficacy (cure rates >90%) will become the norm for the treatment of chronic HCV infection. As such, even moderate treatment uptake and response rates to DAA-based therapy among PWID, HCV treatment as prevention has a high likelihood of achieving substantial reductions in HCV prevalence among PWID and thereby potentially prevent transmissions. The Gilead Sciences interferon (IFN)-free dual DAA regimen of sofosbuvir (SOF) 400 mg once-daily (SOF, nucleotide polymerase inhibitor) and velpatasvir 100 mg once-daily (VEL, NS5A inhibitor) has demonstrated high efficacy (95-96% SVR12) with a treatment duration of 12 weeks in treatment-naïve prisoners with HCV genotypes 1-6 and is currently in phase III evaluation as a 12 week regimen. The availability of a simplified IFN-free DAA-based once-daily pangenotypic regimen of SOF/VEL should considerably enhance the capacity to scale-up HCV treatment among PWID and other high-risk populations such as prisoners. One setting that provides opportunity to assess the feasibility of HCV treatment as prevention is in correctional centres. Very close relationships exist between illicit and injecting drug use, imprisonment

	and the prevalent blood-borne virus (BBV) infections in prisoners - notably HCV and hepatitis B virus (HBV) infection. PWID have high rates of imprisonment predominantly due to the illegal nature of drug use, and the imperative to fund drug dependence through crime. Indeed, almost half of all Australian prisoners report injecting drug use and approximately 70% are incarcerated for drug-related crimes. Given this nexus, HCV infection is very common among prisoners with an overall prevalence of 30%, and up to 80% among IDUs. Correctional centres represent a significant public health opportunity to assess the feasibility of HCV treatment as prevention with the aim of reducing the spread of HCV in the correctional and community settings.
Study objectives	A rapid scale-up of HCV treatment with interferon-free DAA therapy among prisoners will achieve a significant reduction in the incidence of HCV infection over a two year period in the correctional setting. Primary objective To evaluate the feasibility and impact of a rapid scale-up of HCV treatment (with interferon-free DAA therapy) on the incidence of HCV infection over a two year period in the correctional setting. Secondary objectives - To evaluate the impact of a rapid scale-up of HCV treatment on the prevalence of HCV infection over a two year period within the correctional setting - To evaluate the proportion of prisoners with viral relapse, defined as undetectable HCV RNA at end of treatment (ETR) and detectable HCV RNA at 12 weeks following the end of treatment - To evaluate the proportion of prisoners with undetectable HCV RNA at 12 weeks following the end of treatment (SVR12) - To evaluate the proportion of prisoners with undetectable HCV RNA at 4 weeks following the end of treatment (SVR4) - To evaluate the proportion of prisoners with an end of treatment response (ETR) - To evaluate the proportion of prisoners adherent to therapy (both on-treatment adherence and treatment discontinuation) and the association between adherence and response to treatment. - To evaluate safety and tolerability - To evaluate the rate of HCV treatment uptake among eligible prisoners and reasons for non-uptake - To evaluate changes in illicit drug use behaviors during treatment - To evaluate the rate of HCV reinfection following treatment - To evaluate prisoner and provider attitudes and barriers towards the provision of treatment of HCV infection using standard therapy as compared to interferon-free DAA therapy in the correctional setting

	- To evaluate the cost-effectiveness of scaling up HCV treatment in the correctional setting, including the benefits on the transmission of HCV in the community. - To establish a sample repository for future HCV-related research
Study design	Initially, two maximum security correctional centres in NSW will be selected. A lead-in HCV incidence and prevalence surveillance phase will precede commencement of the treatment intervention phase at each centre. The study will then be progressively scaled up at a further 2-4 medium security correctional centres. The study consists of four phases as detailed below: **Surveillance of HCV Incidence and Prevalence** The HCV incidence and prevalence surveillance phase is a prospective longitudinal cohort. HCV incidence and prevalence will be monitored through regular six-monthly cross-sectional surveys of Prisoners for up to 4 years. Participation will involve providing informed consent, a blood sample and completing the SToP-C interview. It is estimated that approximately 360 prisoners in each maximum security correctional centre and 160 prisoners in each medium security correctional centre will participate in the surveillance of incidence and prevalence component of the study. **Modelling** The data from year 1 of the surveillance of HCV incidence and prevalence phase will be used to model the number of prisoners required to be treated to demonstrate a significant reduction in incidence (see appendix 2 for more information). **Treatment Intervention** The treatment phase will be progressively introduced at each centre once sufficient surveillance data is collected to characterise HCV incidence and prevalence. The intervention component of this study will consist of an open-label study of interferon-free DAA therapy for the treatment of HCV infection. Prisoners will receive 12 weeks of SOF/VEL in an oral once-daily fixed dose combination. The minimum number of prisoners treated to demonstrate a significant reduction in incidence will be determined during the modelling phase as detailed above, however all prisoners with HCV infection identified in the Surveillance Phase will be offered treatment. **Cost Effectiveness** At enrolment in the surveillance phase and at regular intervals during the treatment intervention phase prisoners will be required to complete a survey to obtain estimates of health outcomes (EQ-5D survey). This data will be used by the health economist to determine the cost effectiveness of treatment as prevention in the correctional setting.
Participant population	Eligibility criteria

	The eligibility criteria for each phase of the study are detailed below (as applicable). **Surveillance of HCV Incidence and Prevalence** *Inclusion criteria* 1) 18 years of age or older. 2) Voluntarily signed the (surveillance phase) informed consent form. 3) Adequate English and mental health status to provide written informed consent and comply with study procedures. *Exclusion criteria* 1) Prisoners of a security classification which makes clinic attendance for study visits logistically difficult **Treatment Intervention** *Inclusion criteria* 1) 18 years of age or older. 2) Voluntarily signed the (treatment phase) informed consent form. 3) Detectable HCV RNA in plasma. 4) HCV genotypes 1-6 5) Compensated liver disease where the following criteria must be met: a. INR< 1.8 b. Albumin >30 g/L c. Total Bilirubin <35umol/L 6) Prisoners with Fibroscan > 12KPa or AFP >50 ng/mL must be referred for an abdominal ultrasound or CT scan 7) Negative pregnancy test at baseline (females of childbearing potential only). 8) [For prisoners released during treatment or follow-up] If engaging in sexual intercourse which may potentially result in pregnancy, all fertile males must be using effective contraception during treatment and during the 90 days after treatment end, and all fertile females must be using effective contraception during treatment and during the 30 days after treatment end. 9) If co-infection with HIV is documented, the subject must meet the following criteria: a. Antiretroviral (ARV) untreated for >8 weeks preceding screening visit with CD4 T cell count >500 cells/mm^3 OR b. On a stable ARV regimen for >8 weeks prior to screening visit, with CD4 T cell count >200 cells/mm^3 and an undetectable plasma HIV RNA level. • Suitable ARV include: ○ Nucleos(t)ide reverse transcriptase inhibitors: Tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), emtricitabine (FTC)Non-nucleoside reverse transcriptase inhibitors: Rilpivirine ○ Protease inhibitors: Atazanavir, darunavir, lopinavir, ritonavir

	○ Integrase inhibitors: Dolutegravir, raltegravir, elvitegravir/cobicistat • Contraindicated ARV include: ○ Efavirenz (50% reduction in velpatasvir exposure) ○ Didanosine ○ Zidovudine ○ Tipranavir Other ARV agents may be permissible at the time of study commencement pending further drug-drug interaction studies; please discuss with the Medical Monitor. <u>*Exclusion criteria*</u> 1) Therapy with any systemic anti-viral, anti-neoplastic or immunomodulatory treatment (including supraphysiologic doses of steroids and radiation) ≤6 months prior to the first dose of study drug. 2) Any investigational drug ≤6 weeks prior to the first dose of study drug. 3) History or other evidence of clinical hepatic decompensation (i.e. ascites, encephalopathy or oesophageal variceal haemorrhage) 4) Solid organ transplant 5) Clinically significant illness (other than HCV) or any other major medical disorder that may interfere with the prisoner treatment, assessment or compliance with the protocol; prisoners currently under evaluation for a potentially clinically significant illness (other than HCV) are also excluded. 6) History of any of the following: a. Malignancy within 5 years prior to screening, with exception of specific cancers that may have been cured by surgical resection (basal cell skin cancer, etc.). Subjects under evaluation for possible malignancy are also excluded. b. Significant drug allergy (such as anaphylaxis or hepatotoxicity). 7) Any of the following lab parameters at screening: a. ALT > 10 x ULN b. AST > 10 x ULN c. Total bilirubin >35µmol/L d. Platelets < 50,000/µL e. Creatinine clearance (CL_{cr}) < 60 mL/min f. Haemoglobin < 11 g/dL for females ; < 12 g/dL for males g. Albumin < 30g/L h. INR > 1.5 ULN unless subject has known haemophilia or is stable on an anticoagulant regimen affecting INR 8) Chronic use of systemically administered immunosuppressive agents (e.g. prednisone equivalent > 10 mg/day) 9) Known hypersensitivity to VEL, SOF or formulation excipients. 10) Use of prohibited concomitant medications as described in section 6.2

	11) Pregnant or nursing female 12) Ongoing severe psychiatric disease as judged by the treating physician. 13) Frequent injecting drug use that is judged by the treating physician to compromise treatment safety. 14) Inability or unwillingness to provide informed consent or abide by the requirements of the study. 15) Any other criteria that is judged by the treating physician to potentially compromise treatment safety.
Treatment of participants	All prisoners with detectable HCV RNA identified through the surveillance of HCV incidence and prevalence will be offered treatment. Data from the surveillance phase and prisoner movements in and out of each correctional centre will be used to mathematically model the number of HCV RNA positive prisoners needed to be treated in order to achieve the primary endpoint. Prisoners will receive 12 weeks of SOF/VEL in an oral once-daily fixed dose combination. Prisoners may be dispensed medication daily or up to weekly at the nurse and/or clinician's discretion and in accordance with standard Justice Health & Forensic Mental Health Network (JH&FMHN) dispensing policies and procedures at each participating centre. Data on missed doses will be collected to monitor adherence. Prisoners who become reinfected during the treatment phase will be offered a further 12 week course of SOF/VEL in an oral once-daily fixed dose combination.
Study procedures	**Surveillance of HCV Incidence and Prevalence** Prisoners will have 6-monthly blood borne virus screening and interviews (please refer to Study Flow Chart – Incidence and Prevalence Surveillance). Prisoners identified as having HCV infection will be invited to receive SOF/VEL therapy once the treatment phase commences at that correctional centre. **Treatment Intervention** Prisoners must provide written informed consent and meet treatment eligibility at screening. Regular HCV virology, safety bloods, interviews, and assessment of concomitant medications and adverse events will be completed (please refer to Study Flow Chart – Treatment Phase).
Statistics	**Primary endpoints:** 1. A significant reduction in HCV incidence within the network of participating correctional centres **Secondary endpoints:** 1. Reduction in chronic HCV prevalence 2. Viral relapse defined as the proportion of prisoners with undetectable HCV RNA at end of treatment (week 12) but

	detectable HCV RNA at 12 weeks post end of treatment (week 24) 3. SVR12 defined as the proportion of prisoners with undetectable HCV RNA at 12 weeks post end of treatment (week 24) 4. SVR4 defined as the proportion of prisoners with undetectable HCV RNA at 12 weeks post end of treatment (week 16) 5. ETR defined as the proportion of prisoners with undetectable HCV RNA at end of treatment (week 12) 6. Proportion adherent to therapy (on-treatment adherence and treatment discontinuation) 7. Rate of HCV reinfection during and following treatment 8. Rate of treatment uptake in prisoners identified as HCV RNA positive in the surveillance phase 9. Change in illicit drug use during treatment 10. Change in mental health during treatment 11. Change in health utility during treatment HCV incidence will be calculated using person-time methods. 12. Change in prisoner and provider attitudes and barriers towards HCV treatment with DAA-based therapy in the correctional centre setting New prisoners are continuously enrolled to replace those who leave each correctional centre. HCV incidence will be assessed during the surveillance phase which covers pre-treatment, on-treatment, and post-treatment periods. Tests for differences over time periods will be performed using Poisson and other regression models. Based on a conservative estimated enrolment of 720 prisoners across the prison network, 468 will be uninfected (i.e., at-risk) for HCV (35% chronic HCV prevalence). With an expected incidence rate of 15 per 100 person years, the study has 90% power to detect a hazard ratio (HR) of the effect of SOF/VEL treatment on reducing HCV incidence of ≤0.65 (i.e., 35% reduction in incidence or greater) as statistically significant (two sided α=0.05). An initial evaluation of pre-treatment HCV incidence will be undertaken once 200 person years of pre-treatment follow-up have been achieved. These interim HCV incidence outputs will be used to inform additional modelling to determine the need for enhanced enrolment. Available data will also evaluate the extent of time in study, as relatively high rates of prisoner release and transfer (higher in medium than maximum security prisons) are anticipated. This data will also determine need for enhanced enrollment. HCV incidence rates will be calculated using Kaplan-Meier methods and compared using log-rank tests. Treatment outcomes will be summarised with 95% CI using exact methods if indicated. Both intention to treat and per protocol analyses will be performed. The per protocol study population is defined as prisoners who receive >80% of planned

	treatment and have a SVR12 result available. A final full statistical analysis plan will be written and signed off by the Protocol Steering Committee prior to final study data lock.

Study Flow Chart – Incidence and Prevalence Surveillance

Assessment / Procedure	Enrolment	6 monthly FU (+/- 3 months)
Informed consent	x	
Behavioural Interview (Enrolment)	x	
Behavioural Interview (Follow-up)		x
EQ-5D survey	x	x
HCV antibody	x	x
HCV-RNA testing (Taqman)[a]	x	x
HCV Genotype[b]	x	X[f]
HIV antibody	x	x[f]
HBV core antibody	x	x[f]
HBV surface antibody	x	x[f]
HBV surface antigen[c]	x	x[f]
Fibroscan[d] (where available)	x	
Stored EDTA plasma	x	x
Buffy Coat	x	
PBMCs[e]	x	

[a] if HCV antibody positive, [b] if HCV RNA positive, [c] if HBV antibody positive, [d] if HCV RNA positive, [e] to be collected on individuals with negative HCV Ab and RNA and at high risk of blood borne virus infection only, [f] if HCV incident case

Study Flow Chart – Treatment Phase

Assessment / Procedure	Screen	BSL	WK4	WK8	ETR	SVR4	SVR12
Study weeks	**-12 to 0**	**0**	**4**	**8**	**12**	**16**	**24**
Study days	**-84 to 0**	**0**	**28**	**56**	**84**	**112**	**168**
Visit windows (days)			**+/- 7**	**+/- 7**	**+/- 7**	**+/-7**	**+/-14**
Informed consent	x						
Medical History[a]	x						
Physical measurements	x						
Fibroscan (where available)	X[b]						x[c]
Behavioural Interview (Enrolment)							
Behavioural Interview (Follow-up)	x				x		x
Psychiatric Survey (Kessler 10)	x				x		x
Adherence			x	x	x		
EQ-5D	x				x		x
HCV-RNA testing (Taqman)	x		x		x		x
Liver function tests	x	x	x		x		x
Full blood count	x	x	x		x		x
Biochemistry	x	x	x		x		x
Clotting	x						
HBV and HIV serology							x
Pregnancy test (serum or urine)[e]	x	x	x	x	x	x	
Concomitant medication[d]	x	x	x	x	x		
Adverse events		x	x	x	x	x	
Stored EDTA plasma	x		x		x		x

[a]including a targeted mental health assessment, [b]Fibroscan performed at screening for prisoners without valid Fibroscan result in past 12 months only, [c]Fibroscan at SVR12 not performed for prisoners with $F_0/F_1/F_2$ score at screening, [d]HIV, drug dependency and neuropsychiatric medications only, [e]female prisoners of childbearing potential only.

1.0 Background and rationale

The global burden of hepatitis C virus (HCV) infection continues to rise. People who inject drugs (PWID) represent the core of the HCV epidemic in developed countries, accounting for the majority of new (80%) and existing (60%) cases[1]. There is no effective vaccine for HCV. Although harm reduction strategies such as needle syringe programs (NSP) and opiate substitution treatment (OST) have been successful for HIV[3], these strategies have limited evidence for HCV prevention and often require a combination of strategies to be successful[4-6].

HCV-related morbidity and mortality also continues to rise[7]. The natural history of chronic HCV (cirrhosis risk escalates after 15-20 years)[8] and ageing cohorts in many countries means that a large burden of advanced liver disease is anticipated in the next decade, particularly among older former and current PWID[9]. Although HCV treatment for PWID has been demonstrated to be safe and effective[10, 11,] treatment uptake remains low[12-15].

In the field of HIV, a finding that has generated considerable excitement is the demonstration that antiretroviral therapy is an effective strategy for the prevention of HIV transmission[16]. In contrast to treatment for HIV, HCV treatment is both curative and circumscribed in duration (as short as 12 weeks) – two key features which hold great promise for the potential effectiveness of HCV treatment as prevention. The potential prevention utility of HCV treatment with the arduous regimen of pegylated interferon and ribavirin for active PWID using has been demonstrated in a number of mathematical modelling studies[17-24].

Over the next 1-2 years, simple (once-daily), tolerable, short-duration (12-24 weeks) therapy with interferon-free directly acting antivirals (DAA) regimens with extremely high efficacy (cure rates >90%) will become the norm for the treatment of chronic HCV infection[25]. As such, even moderate treatment uptake and response rates to DAA-based therapy among PWID, HCV treatment as prevention has a high likelihood of achieving substantial reductions in HCV prevalence among PWID and thereby potentially prevent transmissions.

The Gilead Sciences IFN-free dual DAA regimen of sofosbuvir 400 mg once-daily (SOF, nucleotide polymerase inhibitor) and velpatasvir 100 mg once-daily (VEL, NS5A inhibitor) has demonstrated high efficacy (95-96% SVR12) with a treatment duration of 12 weeks in treatment-naïve patients with HCV genotypes 1-6 and is currently in phase III evaluation as a 12 week regimen. The availability of a simplified IFN-free DAA-based once-daily pangenotypic regimen of sofosbuvir/velpatasvir (SOF/VEL) should considerably enhance the capacity to scale-up HCV treatment among PWID and other high-risk populations such as prisoners.

One setting that provides opportunity to assess the feasibility of HCV treatment as prevention is in correctional centres. Very close relationships exist between illicit and injecting drug use, imprisonment and the prevalent blood-borne virus (BBV) infections in prisoners - notably HCV and hepatitis B virus (HBV) infection. PWID have high rates of imprisonment predominantly due to the illegal nature of drug use, and the imperative to fund drug dependence through crime. Indeed, almost half of all Australian prisoners report injecting drug use and approximately 70% are incarcerated for drug-related crimes.[26] Given this nexus, HCV infection is very common among prisoners with an overall prevalence of 30%, and up to 80% among IDUs. The static prisoner population in Australia is around 30,000,with upwards of 50,000 people cycling through Australian correctional centres annually, and an ex-prisoner population conservatively estimated at 400,000.[28] Almost all prisoners are eventually released back into the community. To this end, correctional centres represent a significant public health opportunity to assess the feasibility of HCV treatment as prevention with the aim of reducing the spread of HCV in both the correctional setting and broader community.

In Australia, the infrastructure for the surveillance of HCV prevalence and incidence in correctional centres has been established through regular national cross-sectional surveys of prisoners (led by Prof. Butler)[29] and an ongoing multicentre, prospective cohort study of seronegative prisoners in NSW at risk of acute HCV which began in 2005 (led by Prof. Lloyd)[30]. Data from these studies indicate both a high prevalence (51%)[29] and incidence (12 per 100 person-years)[31] of HCV among PWID in the correctional setting. Further, a well-established HCV treatment model (led by Prof. Lloyd)[32] is in place within the New South Wales correctional system (814 prisoners treated since 1995) which has been expanded to include an innovative nurse-led model of care (116 treated in 2012).

The well-established surveillance capacity and HCV treatment infrastructure among correctional centres in New South Wales, Australia, offers a unique opportunity to assess the feasibility of HCV treatment as prevention with interferon-free DAA therapy in correctional centres.

The team is ideally placed to undertake this research. New South Wales has established ongoing surveillance of bloodborne viruses via the Prison Entrants Survey[29] and the HITS cohort[30], both of which are unique internationally. Further, an existing model for HCV treatment within correctional centres is well-established, creating an infrastructure for the scale-up of DAA-therapy in this setting. Lastly, members of the team have international track records in modelling HCV amongst PWID, and the impact and cost-effectiveness of varied HCV prevention interventions including HCV treatment as prevention.

2.0 Hypotheses

A rapid scale-up of HCV treatment with interferon-free DAA therapy among prisoners will achieve a significant reduction in the incidence of HCV infection over a two year period in the correctional setting.

3.0 Study objectives

3.1 Primary objective

To evaluate the feasibility and impact of a rapid scale-up of HCV treatment (with interferon-free DAA therapy) on the incidence of HCV infection over a two year period in the correctional setting.

3.2 Secondary objective(s)

- To evaluate the impact of a rapid scale-up of HCV treatment on the prevalence of HCV infection over a two year period within the correctional setting
- To evaluate the proportion of prisoners with viral relapse, defined as undetectable HCV RNA at end of treatment (ETR) and detectable HCV RNA at 12 weeks following the end of treatment
- To evaluate the proportion of prisoners with undetectable HCV RNA at 12 weeks following the end of treatment (SVR12)
- To evaluate the proportion of prisoners with undetectable HCV RNA at 4 weeks following the end of treatment (SVR4)
- To evaluate the proportion of prisoners with an end of treatment response (ETR)
- To evaluate the proportion of prisoners adherent to therapy (both on-treatment adherence and treatment discontinuation) and the association between adherence and response to treatment
- To evaluate safety and tolerability
- To evaluate the rate of HCV treatment uptake among eligible prisoners and reasons for non-uptake
- To evaluate changes in illicit drug use behaviors during treatment
- To evaluate the rate of HCV reinfection following treatment

- To evaluate prisoners and provider attitudes and barriers towards the provision of treatment of HCV infection using standard therapy as compared to interferon-free DAA therapy in the correctional setting
- To evaluate the cost-effectiveness of scaling up HCV treatment in the correctional setting, including the benefits on the transmission of HCV in the community.
- To establish a sample repository for future HCV-related research

4.0 Study design

Summary of study design

The study consists of four phases as detailed below. Two maximum security correctional centres in NSW will be selected initially. A lead-in HCV incidence and prevalence surveillance phase will precede introduction of the treatment intervention at each centre. The treatment intervention will be scaled up at a further 2-4 medium security correctional centres following the lead-in HCV incidence and prevalence surveillance phase.

4.1 Surveillance of HCV Incidence and Prevalence and Liver Disease Burden

The HCV incidence and prevalence surveillance phase is a prospective longitudinal cohort. HCV incidence and prevalence and liver disease burden will be monitored through regular six-monthly cross-sectional surveys of prisoners for up to 4 years. Participation will involve providing informed consent (at enrolment), a blood sample, fibroscan (where available, for prisoners with current HCV infection) and completing the SToP-C behavioural interview and EQ-5D health outcomes survey. It is estimated that approximately 720 prisoners will participate in the surveillance of incidence and prevalence component of the study.

4.2 Modelling

The data from year 1 of the surveillance of HCV incidence and prevalence phase will be used to model the number of prisoners required to be treated to demonstrate a significant reduction in incidence (see appendix 2 for more information).

4.3 Treatment Intervention

The treatment intervention will be progressively scaled-up in the participating correctional centres. The intervention will consist of a phase II open-label study of interferon-free DAA therapy for the treatment of HCV infection. This will be a 12 week regimen of SOF/VEL in an oral once-daily fixed dose combination. The treatment phase will commence in year 2. It will be sequentially implemented in participating centres. The exact number of prisoners treated to demonstrate a significant reduction in incidence will be determined during the modelling phase as detailed above, however all prisoners participating in the HCV surveillance phase who test positive for HCV infection will be offered participation in the treatment intervention phase. Prisoners must provide separate written informed consent (specific to the treatment intervention phase) prior to commencing treatment in this phase.

4.4 Cost Effectiveness

At enrolment and six-monthly follow-up visits in the surveillance phase and at regular intervals during the treatment intervention phase prisoners will be required to complete a survey to obtain estimates of health outcomes (EQ-5D survey). This data will be used by the health economist to determine the cost effectiveness of treatment as prevention in the correctional setting.

4.5 Sub-studies

Additional sub-studies will be submitted for HREC review as appendices of the protocol.

5.0 Participant population

Eligibility criteria

The eligibility criteria for each phase of the study are detailed below (as applicable).

5.1 Surveillance of HCV Incidence and Prevalence

Inclusion criteria

1) 18 years of age or older
2) Voluntarily signed the (surveillance phase) informed consent form.
3) Adequate English and mental health status to provide written informed consent and comply with study procedures

Exclusion criteria

1) Prisoners of a security classification which makes clinic attendance for study visits logistically difficult

5.2 Treatment Intervention

Inclusion criteria

1) 18 years of age or older.
2) Voluntarily signed the (treatment phase) informed consent form.
3) Detectable HCV RNA in plasma.
4) HCV genotypes 1-6
5) Compensated liver disease where the following criteria must be met:
    a) INR< 1.8
    b) Albumin >30 g/L
    c) Total Bilirubin <35umol/L
6) Prisoners with Fibroscan > 12KPa or AFP >50 ng/mL must be referred for an abdominal ultrasound or CT scan
7) Negative pregnancy test at baseline (females of childbearing potential only).
8) [For prisoners released during treatment or follow-up] If engaging in sexual intercourse which may potentially result in pregnancy, all fertile males must be using effective contraception during treatment and during the 90 days after treatment end, and all fertile females must be using effective contraception during treatment and during the 30 days after treatment end
10) If co-infection with HIV is documented, the subject must meet the following criteria:
    a. Antiretroviral (ARV) untreated for >8 weeks preceding screening visit with CD4 T cell count >500 cells/mm^3

    OR

    b. On a stable ARV regimen for >8 weeks prior to screening visit, with CD4 T cell count >200 cells/mm^3 and an undetectable plasma HIV RNA level.

    - Suitable ARV include:
        - Nucleos(t)ide reverse transcriptase inhibitors: Tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), emtricitabine (FTC)Non-nucleoside reverse transcriptase inhibitors: Rilpivirine
        - Protease inhibitors: Atazanavir, darunavir, lopinavir, ritonavir
        - Integrase inhibitors: Dolutegravir, raltegravir, elvitegravir/cobicistat
    - Contraindicated ARV include:
        - Efavirenz (50% reduction in velpatasvir exposure)
        - Didanosine
        - Zidovudine
        - Tipranavir

    Other ARV agents may be permissible at the time of study commencement pending further drug-drug interaction studies; please discuss with the Medical Monitor.

Exclusion criteria

1) Therapy with any systemic anti-viral, anti-neoplastic or immunomodulatory treatment (including supraphysiologic doses of steroids and radiation) ≤6 months prior to the first dose of study drug.
2) Any investigational drug ≤6 weeks prior to the first dose of study drug.
3) History or other evidence of clinical hepatic decompensation (i.e. ascites, encephalopathy or oesophageal variceal haemorrhage)
4) Solid organ transplant
5) Clinically significant illness (other than HCV) or any other major medical disorder that may interfere with the prisoner treatment, assessment or compliance with the protocol; prisoners currently under evaluation for a potentially clinically significant illness (other than HCV) are also excluded.
6) History of any of the following:
    a. Malignancy within 5 years prior to screening, with exception of specific cancers that may have been cured by surgical resection (basal cell skin cancer, etc.). Subjects under evaluation for possible malignancy are also excluded.
    b. Significant drug allergy (such as anaphylaxis or hepatotoxicity).
7) Any of the following lab parameters at screening:
    a. ALT > 10 x ULN
    b. AST > 10 x ULN
    c. Total bilirubin > 35µmol/L
    d. Platelets < 50,000/µL
    e. Creatinine clearance (CL_{cr}) < 60 mL/min
    f. Haemoglobin < 11 g/dL for females ; < 12 g/dL for males
    g. Albumin < 30g/L
    h. INR > 1.5 ULN unless subject has known haemophilia or is stable on an anticoagulant regimen affecting INR
8) Chronic use of systemically administered immunosuppressive agents (e.g. prednisone equivalent > 10 mg/day)
9) Known hypersensitivity to VEL, SOF or formulation excipients.
10) Use of prohibited concomitant medications as described in section 6.2
11) Pregnant or nursing female
12) Ongoing severe psychiatric disease as judged by the treating physician.
13) Frequent injecting drug use that is judged by the treating physician to compromise treatment safety.
14) Inability or unwillingness to provide informed consent or abide by the requirements of the study.
15) Any other criteria that is judged by the treating physician to potentially compromise treatment safety.

6.0 Treatment of participants

6.1 Treatment

Prisoners will receive 12 weeks of open-label sofosbuvir/velpatasvir (SOF/VEL, 400 mg/100mg daily) in an oral once-daily fixed dose combination. Dose modifications are prohibited.

All prisoners with detectable HCV RNA identified through the surveillance of HCV incidence and prevalence phase will be offered treatment, once the treatment intervention phase commences at that correctional centre. The number of prisoners which need to be treated to achieve a significant reduction in HCV incidence will be modelled. Prisoners with detectable HCV RNA identified through the surveillance of HCV incidence and prevalence phase may also elect at any time to have the current standard of care therapy available at that centre outside of participation in the study's treatment intervention phase.

Prisoners' 12-week therapy will be followed by a 12 week follow-up period to determine whether the subject has achieved a sustained virological response at 4 and 12 weeks post treatment completion (SVR4 and SVR12 respectively). Medical hold will be requested for the duration of treatment. Where

prisoners are transferred to a correctional centre not included in the study the Nursing Unit Manager at that centre will be contacted to arrange transfer of study drug and follow-up care to be provided by the JH&FMHN Hepatitis Service. Where prisoners are unexpectedly released into the community whilst on treatment, all possible efforts will be made to arrange delivery of remaining doses of study drug to prisoners and refer appropriate services for continuity of care.

Prisoners may be dispensed medication daily or up to weekly at the nurse and/or clinician's discretion. The treatment will be administered via directly observed therapy or provided to the prisoner for self-administration, according to the nurse and/or clinician's discretion and standard Justice Health & Forensic Mental Health Network (JH&FMHN) dispensing policies and procedures at each participating site. Data on missed doses will be collected to monitor adherence.

Prisoners who are reinfected following treatment and during the follow-up period of the surveillance phase will be offered a further 12 week regimen of the study drug whilst the treatment phase remains open at that centre.

6.2 Prior and concomitant medications

Concomitant medication must be recorded in the source documents and electronic case report form (eCRF) from screening until the last dose of study medication. Only HIV, neuropsychiatric therapies and treatments for drug dependency will be recorded in the concomitant medications form in the eCRF. Illicit drug use should not be recorded on the concomitant medications form as information about this will be captured in the behavioural questionnaire.

The following medications are prohibited from **28 days prior to the baseline visit** through to the end of treatment:

- Haemotologic stimulating agents (e.g. erythropoiesis-stimulating agents (ESAs); granulocyte colony stimulating factor (GCSF); thrombopoietin (TPO) mimetics)
- Chronic systemic immunosuppressants including, but not limited to, corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine, or monoclonals antibodies (e.g. infliximab)
- Investigational agents or devices for any indication
- Drugs disallowed per prescribing information of SOF

Concomitant use of certain medications or herbal/natural supplements (such as substrates, inhibitors or inducers of drug transporters or metabolizing enzymes, eg, P-gp or CYP3A) with study drug may result in pharmacokinetic interactions resulting in increases or decreases in exposure of study drug or these medications. The use of the "Disallowed" agents in Table 1 is prohibited from 21 days prior to Baseline through to the end of treatment.

Examples of representative medication which are prohibited or are used with caution are listed below:

Table 1: List of Disallowed Medications

Drug Class	Agents Disallowed	Use with Caution
Acid Reducing Agents[a]		H2-Receptor Antagonists[a], Antacids[a], Proton-Pump Inhibitors[a]
Anticonvulsants[b]	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	
Antimycobacterials[b]	Rifabutin, Rifapentine, Rifampin	
Antiretrovirals	Efavirenz[b]	

Cardiac Medications[c]	Amiodarone[e]	Diltiazem, Verapamil, Dronedarone, Ranolazine, Bosentan, Olmesartan, Valsartan, Telmisartan, Quinidine, Digoxin[f]
Herbal/Natural Supplements[b]	St. John's Wort, Echinaccea, Milk Thistle (i.e. silymarin), Chinese herb Sho-Saiko-To (or Xiao-Shai-Hu-Tang)	
HMG-CoA Reductase Inhibitors[d]		Rosuvastatin (≤ 10 mg/day), Atorvastatin, Simvastatin, Pravastatin, Pitavastatin, Fluvastatin, Lovastatin
Other	Modafinil[b], sulfasalazine[c], methotrexate[c]	

[a] H2-receptor Antagonists must not exceed a dose of 20 mg famotidine or equivalent and can be taken simultaneously with SOF/VEL and/or staggered by 12 hours. Antacids that directly neutralize stomach acid (i.e. Tums, Maalox) may not be taken within 4 hours (before or after) of SOF/VEL administration. Proton pump inhibitors equivalent to omeprazole 20 mg can be taken simultaneously with SOF/VEL in the fed state.

[b] May result in a decrease in the concentration of study drugs

[c] may result in an increase in the concentration of study drugs and/or concomitant medications

[d] Use with SOF/VEL may result in an increase in the concentration of HMG-CoA Reductase Inhibitors. Monitor for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis

[e] May result in symptomatic bradycardia. Mechanism is not currently known. The use of amiodarone is prohibited from 60 days prior to Baseline/Day 1 through the end of treatment

[f] Monitor for signs and symptoms of digoxin toxicity

Should any prisoner need to initiate treatment with any excluded concomitant medication during the study, the Medical Monitor, Professor Gregory Dore must be consulted prior to the initiation of any excluded medication. In the event that an excluded medication is initiated prior to discussion with Professor Gregory Dore, he must be made aware of the use of the excluded medication as soon as possible.

7.0 Study procedures

7.1 Surveillance of HCV Incidence and Prevalence

The following procedures will be performed for prisoners enrolled in the surveillance of incidence and prevalence phase of the study:

7.1.1 Enrolment

- Informed consent
- Fibroscan (where available)
- Behavioural interview (enrolment)
- Health outcomes survey (EQ-5D)
- Pre and post test counselling
- Sample collection (10ml EDTA plasma) for HCV antibody, HCV RNA and HCV genotype testing.
- Sample collection for (10ml SST) for HIV antibody, HBV surface antibody, HBV core antibody and HBV surface antigen.
- Research sample collection (10ml EDTA plasma) for plasma and buffy coat storage.
- Research sample collection (60ml ACD) for PBMC collection*

* to be collected on individuals with negative HCV Ab and RNA and at high risk of blood borne virus infection only

7.1.2 Follow-up (6 monthly, +/- 3 months)

- Behavioural interview (follow-up)
- Health outcomes survey (EQ-5D)
- Pre and post test counselling

- Sample collection (10ml EDTA plasma) for HCV antibody, HCV RNA and HCV genotype testing. Genotype will be tested for incident/reinfection cases only.
- If HCV incident case identified, sample collection (10ml SST) for HIV antibody, HBV surface antibody, HBV core antibody and HBV surface antigen.
- Research sample collection (10ml EDTA plasma) for plasma storage.

Prisoners in the surveillance phase identified as having chronic HCV infection will be invited to receive 12-week SOF/VEL treatment for HCV.

7.2 Treatment Intervention

7.2.1 Initial screening period (day -84 to day 0)

- Informed consent
- Medical history including a targeted mental health assessment
- Physical measurements
- Fibroscan (where available)
- Behavioural interview (enrolment)
- Psychiatric survey (Kessler10)
- Health outcomes survey (EQ-5D)
- Liver function tests, Full blood count Biochemistry and Clotting
- Concomitant medication
- HCV Virology sample collection (10ml EDTA plasma) for HCV RNA testing
- Research sample collection (10ml EDTA plasma) for plasma

7.2.2 Baseline visit (day 0)

- Liver function tests, Full blood count and Biochemistry
- Concomitant medication
- Adverse events

Prisoners must complete the baseline visit and commence treatment within 6 weeks of screening assessments.

7.2.3 On Treatment - Week 4, 8 (+/- 7 days)

- Adherence
- Liver function tests, Full blood count and Biochemistry
- Concomitant medication
- Adverse events
- HCV Virology sample collection (10ml EDTA plasma) for HCV RNA
- Research sample collection (10ml EDTA plasma) for plasma storage (W4 only)

7.2.4 End of Treatment (ETR) (+/- 7 days)

- Behavioural interview (follow-up)
- Psychiatric survey (Kessler10)
- Adherence
- Health outcomes survey (EQ-5D)
- Liver function tests, Full blood count and Biochemistry
- Concomitant medication
- Adverse events
- HCV Virology sample collection (10ml EDTA plasma) for HCV RNA
- Research sample collection (10ml EDTA plasma) for plasma storage

7.2.5 Post Treatment Follow-up

SVR4 (week 16, +/- 3 days) and SVR12 (week 24, +/-14 days)

- Fibroscan (SVR 12 only)
- Behavioural interview (follow-up) (SVR 12 only)
- Psychiatric survey (Kessler10) (SVR 12 only)
- Health outcomes survey (EQ-5D) (SVR 12 only)
- Liver function tests, Full blood count and Biochemistry (SVR 12 only)
- HIV and HBV serology (SVR 12 only)
- Adverse events (SVR4 only)
- HCV Virology collection (10ml EDTA plasma) for HCV RNA (SVR 12 only)
- Research sample collection (10ml EDTA plasma) for plasma storage (SVR 12 only)

Table 2: Lab parameters

Biochemistry	Creatinine, urea, uric acid*, calcium*, phosphorus*, cholesterol*, glucose*, sodium, chloride, potassium and bicarbonate
Liver Function Tests	ALT, AST, GGT, total bilirubin, albumin, alkaline phosphatase, total protein
Full Blood Count	Haemoglobin, platelets, white blood cells, and differential white cell count: neutrophils, eosinophils, lymphocytes
Clotting	PT or INR*
HCV Virology	Quantitative (Taqman), genotype
Serology	HCV Ab, HBcAb, HBsAb, HBsAg
HCG Pregnancy Test	For women of childbearing potential, a negative urine (or serum) HCG test at screening and baseline

*Required at screening only

The Behavioral Interview

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

- Demographics/drug treatment history
- Drug and alcohol usage
- Injecting practices and other HCV risk behaviours

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

Kessler 10 (K10)

The Kessler (K10) measure is a 10-item self-report questionnaire intended to yield a global measure of "psychological distress" based on questions about the level of anxiety and depressive symptoms in the most recent 4-week period.

Health Outcomes Survey (EQ-5D)

The EQ-5D 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

Adherence to the SOF/VEL regimen will be assessed by self-report (if self-administered and/or pill count.

7.3 Withdrawal of study participants

Prisoners who cease study medication will, wherever possible, continue to be followed up according to the protocol study plan. Prisoners may revoke consent for follow-up without jeopardising their

relationship with either their doctor, nurse or the UNSW. If a prisoner revokes consent then, if possible, all assessments scheduled for the final visit should be completed.

8.0 Recording and reporting Adverse Events (AEs)

Adverse events and adverse drug reactions may occur in the course of this study. These events may also occur in screened prisoners during the screening period prior to enrolment as a result of protocol-specified interventions. All such events will be recorded at each study visit during treatment and at SVR4 on the adverse event case report form.

8.1 Adverse Event definition

The definition of an adverse event is any untoward medical occurrence in a prisoner administered with a pharmaceutical product which does not necessarily have a causal relationship with the product. Where adverse events are related to the drug, they may be referred to as Adverse Drug Reactions.

Pre-existing conditions or diseases that occur during the study (e.g. seasonal allergies, asthma or recurrent headaches) should not be considered as adverse events unless they change in frequency or severity.

8.2 Assessment and Documentation of Adverse Events

The investigator or co-investigator should assess each adverse event for the following and record their assessment in the medical record:

Severity

Mild	discomfort but no interference with normal daily activity.
Moderate	discomfort sufficient to reduce or affect normal daily activity
Severe	incapacitating with inability to work or perform normal daily activity
Life Threatening	represents an immediate threat to life

Relationship

The relationship of the adverse event to the treatment should be assessed using the following criteria:

PROBABLE (must have first three)

This category applies to those adverse experiences which are considered, with a high degree of certainty, to be related to the test drug. An adverse experience may be considered probable if:

1. It follows a reasonable temporal sequence from administration of the drug.
2. It could not be reasonably explained by the known characteristics of the prisoner's clinical state, environmental or toxic factors, or other modes of therapy administered to the prisoner.
3. It disappears or decreases on cessation or reduction in dose. (There are important exceptions when an adverse experience does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists; e.g., 1) bone marrow depression; 2) tardive dyskinesias.)
4. It follows a known pattern of response to the suspected drug.
5. It reappears upon rechallenge.

POSSIBLE (must have first two)

This category applies to those adverse experiences in which the connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An adverse experience may be considered possible if, or when:

1. It follows a reasonable temporal sequence from administration of the drug.
2. It may have been produced by the prisoner's clinical state, environmental or toxic factors, or their modes of therapy administered to the prisoner.

3. It follows a known response pattern to the suspected drug.

REMOTE (must have first two)

In general, this category is applicable to an adverse event which meets the following criteria:

1. It does not follow a reasonable temporal sequence from administration of the drug.
2. It could readily have been produced by the prisoner's clinical state, environmental or toxic factors, or other modes of therapy administered to the prisoner.
3. It does not follow a known response pattern to the suspected drug.
4. It does not reappear or worsen when the drug is readministered.

UNRELATED

This category is applicable to those adverse experiences which, after careful medical consideration at the time of evaluation, are judged to be clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under REMOTE, POSSIBLE or PROBABLE.

Table for Determining Adverse Events Relationship to Investigational Product				
	Probable	Possible	Remote	Unrelated
Clearly due to extraneous causes	-	-	-	+
Reasonable temporal association with drug administration	+	+	-	-
May be produced by subject's clinical state, etc.	-	+	+	+
Known response pattern to suspected drug	+	+	-	-
Disappears or decreases on cessation or reduction in dose	+	-	-	-
Reappears on rechallenge	+	-	-	-

8.3 Laboratory Test Abnormalities

Laboratory test value abnormalities as such should be reported as adverse events only if the laboratory abnormality meets any one or more of the following criteria:

- Is considered to be a serious adverse event (SAE)
- Results in discontinuation or modification of study treatment
- Results in a requirement for additional concomitant treatment or a modification of current concomitant treatment already given for a laboratory abnormality noted at screening or baseline

As best as possible, the term entered on the CRF should be the condition represented by the laboratory abnormality, not the abnormality itself.

8.4 Serious Adverse Event (SAE) (this includes Serious Adverse Drug Reactions)

The definition of a SAE is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
  (Note: the term "life-threatening" in the definition of "serious" refers to an event/reaction in which the prisoner was at risk of death at the time of event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe)
- requires in-patient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity,

- is a congenital anomaly/birth defect. or
- is a medically important event or reaction

8.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

The Project Team in collaboration with the Medical Officer will review and identify all serious events which fit the criteria of a SUSAR and requiring expedited reporting to relevant parties.

The definition of a SUSAR is a serious adverse event which is both suspected as being related to the drug (i.e. has a reasonable suspected causal relationship and is unexpected) and where the nature and severity is not consistent with known information (e.g. the Investigator's Brochure for an unapproved investigational product or Product Information for an approved) about the drug in question.

8.6 Reporting Requirements

8.6.1 Adverse Events

Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to reporting requirements and within the time periods specified in the protocol.

8.6.2 Serious Adverse Events

All serious adverse events (SAEs) should be reported within 48 working hours to the sponsor by telephone, email, fax or eCRF except for those SAEs that the protocol or other document (e.g. Investigator Brochure) identifies as not needing immediate reporting. The appropriate Serious Event form should be used. Immediate reports should be followed promptly by detailed, written follow-up reports when all information is not included in the initial report. The immediate and follow up reports should identify prisoners by unique code numbers assigned to study prisoners rather than personal identification. The investigator must also comply with all applicable ethical and regulatory requirement/s relating to the reporting of serious adverse events.

Any serious adverse event that is ongoing at the post-study follow-up visit/s must be followed until resolution or until the event stabilizes (for those events that will not resolve).

For deaths, the Principal Investigator will supply the sponsor and the IRB/IEC with any additional requested information (e.g. death certificate, autopsy reports and medical reports).

SAE reports must be faxed to: **Kirby Institute: +61 2 9385 9214**

The Kirby Institute will report all serious adverse reactions related to the Drug (SARs) and Special Situation Reports (SSRs) (see section 8.6.3) with respect to the Drug, occurring during the Study to Gilead DSPH within 15 calendar days of first becoming aware of any such event and in accordance with applicable laws, rules, regulations and guidance.

8.6.3 Special Situation Reports

Special Situation Reports are defined as:

a) Pregnancy Reports,

b) Reports of Medication Error, Abuse, Misuse, or Overdose,

c) Lack of Effect Reports,

d) Reports of ARs in infants following exposure from breastfeeding,

e) Reports of ARs associated with Product Complaints and

f) Reports arising from Occupational Exposure.

8.6.4 Suspected Unexpected Serious Adverse Reaction

The sponsor must expedite the reporting of all SUSARs to all concerned investigators/institutions, IRB/IEC/s, and regulatory authorities within the reporting timeframe. Reports must comply with the applicable regulatory requirements and ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Researchers must inform the IRB/IEC and regulatory authorities of all SUSARs that occur during the study that may affect the conduct of the study or the safety of the prisoners or their willingness to continue participation in the study. Researchers must inform the IRB/IEC as soon as possible of any new information from other published or unpublished studies which may have an impact on the continued ethical acceptability of the study or which may indicate the need for amendments to the study protocol.

9.0 Packaging, labeling, storage and accountability of clinical trial supplies

All study drug will be provided by Gilead Sciences, Inc and should be dispensed under the supervision of the investigator or a qualified member of the investigational staff, or by a clinic pharmacist.

Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects.

A designated person at the study site must receive clinical trial supplies. That person must check that the supplies are in good condition and are complete as per the shipping records. Drugs must be stored in a secure location with limited access. Clinical trial supplies must only be dispensed according to the protocol and records must be kept detailing supplies received, dispensed to the prisoner, returned from the prisoner and returned to the sponsor or destroyed at site, as applicable.

Prisoners may be dispensed medication daily or up to weekly at the nurse and/or clinician's discretion and in accordance with Justice Health & Forensic Mental Health Network dispensing policy. Prisoners will be instructed to return all study drug containers (including empty ones) to the site staff during the course of the study and all containers must be retained for review by the sponsor's monitor until the end of the study.

9.1 Formulation

The SOF/VEL (400mg/100mg) tablets are pink, diamond shaped, film-coated tablets, debossed with "GSI" on one side and "7916" on the other side. In addition to the active ingredient, SOF/VEL tablets also contain the following inactive ingredients: copovidone, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc and iron oxide red.

9.2 Packaging and Labelling

SOF/VEL 400mg/100mg tablets are packaged in bottles containing 28 tablets each. Where more than daily doses are dispensed to prisoners, this will be packaged in labelled prisoner-specific plastic wallets in accordance with Justice Health & Forensic Mental Health Network dispensing policy and procedures.

9.3 Storage and handling

SOF/VEL bottles should be stored at controlled room temperature until required for administration. Controlled room temperature is defined at 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F).

All drug products should be stored in a securely locked area, assessable only to authorized site personnel.

9.4 Dosage and administration

SOF/VEL is to be administered once daily with or without food. Each subject must be given instructions to maintain approximately the same daily dosing interval between study drug doses. Subjects should be instructed to swallow the study medication tablet whole.

For a missed dose of study medication, subjects should be instructed to take the missed dose of study medication as soon as possible during the same day. However, no more than the daily dose of SOF/VEL should be taken on any calendar day. Subjects should be cautioned never to double the next dose with a missed dose of study drug under any circumstances.

10.0 Biological samples

10.1 Laboratory supplies and sample processing

Liver function tests, Full blood count, Biochemistry and Blood Bourne Virus (BBV) serology (HAV, HBV and HIV) will be processed at the local laboratory.

All HCV related tests including HCV antibody, HCV RNA and HCV genotypes will be performed at the central laboratory. Research Samples will also be stored as per the schedule of assessments. All research samples must be stored at -70°C in a temperature monitored freezer. Any temperature deviations above -60°C must be reported to The SToP-C Project Coordinator immediately.

10.2 Surveillance of incidence and prevalence

Enrolment:

- 10ml EDTA plasma for HCV Antibody, HCV RNA and HCV Genotype testing
- 10ml EDTA plasma for stored research plasma and buffy coat
- 10ml SST plasma for HIV antibody, HBV core antibody, HBV surface antibody, HBV surface antigen

6 monthly Follow-up:

- 10ml EDTA plasma for HCV Antibody, HCV RNA and HCV Genotype testing
- 10ml EDTA plasma for stored plasma
- 10ml SST for HIV antibody, HBV core antibody, HBV surface antibody, HBV surface antigen (for HCV incident cases)

10.3 Treatment Intervention

Screening:

- 10ml EDTA plasma for HCV RNA
- 10ml EDTA plasma for stored plasma

On treatment: (W4)

- 10ml EDTA plasma for HCV RNA
- 10ml EDTA plasma for stored plasma

Post treatment: (ETR, SVR4 and SVR12)

- 10ml EDTA plasma for HCV RNA (all visits)
- 10ml EDTA plasma for stored plasma (ETR and SVR12)
- 10ml SST plasma for HIV antibody, HBV core antibody, HBV surface antibody, HBV surface antigen (SVR12 only)

10.4 Transport of biological samples

All site staff handling, packaging, shipping and/or transporting biological samples must understand and comply with regulations relating to the handling and shipping of hazardous goods and/or diagnostic specimens.

11.0 Statistics

The primary endpoint for the treatment-as-prevention evaluation is a significant relative reduction in HCV incidence within the network of participating correctional centres. Secondary outcome measures include: reduction in chronic prevalence; SVR rates; treatment uptake rate; adherence to therapy; changes in risk behaviour during and following treatment; rate of viral relapse; and rate of re-infection. HCV incidence will be calculated using person-time methods.

New prisoners will be continuously enrolled to replace those who leave the participating correctional centres. HCV incidence will be assessed during the surveillance phase which covers pre-treatment, on-treatment and post-treatment periods. Tests for differences over time periods will be performed using Poisson and other regression models.

Based on a conservative estimated enrolment of 720 prisoners across the prison network, 468 will be uninfected (i.e. at-risk) for HCV (35% chronic HCV prevalence). With an expected incidence rate of 15 per 100py, the study has 90% power to detect a hazard ratio (HR) of the effect of SOF/VEL treatment on reducing HCV incidence of ≤0.65 (i.e. 35% reduction in incidence or greater) as statistically significant (two sided α=0.05). An initial evaluation of pre-treatment HCV incidence will be undertaken once 200 person years of pre-treatment follow-up have been achieved. These interim HCV incidence outputs will be used to inform additional modelling to determine the need for enhanced enrolment.

Available data will also evaluate the extent of loss to follow-up, as relatively high rates of prisoner release and transfer (higher in medium than maximum security prisons) are anticipated. This data will also determine need for enhanced enrollment.

HCV incidence rates will be calculated using Kaplan-Meier methods and compared using log-rank tests. Treatment outcomes will be summarised with 95%CI using exact methods if indicated. Both intention to treat and per protocol analyses will be performed. The per protocol study population is defined as prisoners who receive >80% of planned treatment and have a SVR12 result available.

A final full statistical analysis plan will be written and signed off by the Protocol Steering Committee prior to final study data lock.

An interim evaluation of treatment outcomes (end of treatment, SVR4 and SVR12), HCV incidence, injecting risk behavior within the last 30 days will be conducted when the first 50 subjects have either completed the end of treatment (EOT) visit or dropped out of the study (including transferred and released prisoners). Additional DSMB meetings will be scheduled at a frequency commensurate with the risk as determined by the DSMB.

12.0 Data Safety and Monitoring Board (DSMB)

A data safety monitoring board (DSMB) will consist of at least one statistician, at least one practicing gastroenterologist/infectious diseases specialists, 1 epidemiologist or public health specialist and a community representative. Following the first interim analysis involving the first 50 subjects, the DSMB will continue to evaluate adherence, efficacy, HCV incidence and risk behavior on an annual basis, unless significant concerns are identified that trigger more frequent evaluation.

13.0 Data collection, source documents and record retention

The institutions 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 case report forms (eCRF). The Principal Investigator is responsible for ensuring the data collected are complete, accurate and recorded in a timely manner.

13.1 Submission of data

Following each participant visit, the Principal Investigator or designated site staff member will submit the eCRF. Data will then be reviewed for completeness and accuracy and any discrepancies will be notified to the Principal Investigator or designee 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; prisoner medical records, laboratory reports, X-rays, radiologist reports, prisoner diaries, biopsy reports, ultrasound images, prisoner progress notes, pharmacy records and any other reports or records of procedures performed in accordance with the protocol.

The case report form may act as the source document for the following study procedures: Behavioral interview, Kessler-10, EQ-5D and Adherence questionnaire. It is not acceptable for the CRF to be the only record of study participation and progress must also be recorded in the 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. During treatment the Principal Investigator or treatment nurse will review lab reports for abnormalities. If the treatment nurse identifies any abnormalities these will be discussed with the Principal Investigator who will make any clinical management decisions required.

The sponsor's monitor may visit the sites to conduct source document verification. The number of visits will depend upon study complexity, access to the sites and recruitment rate.

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.

13.2 Archiving

The investigator must retain all study documents for 15 years following completion of the trial. The investigator is responsible for ensuring that trial records are not accidentally destroyed and it may be necessary to clearly label prisoner medical records to ensure that they are not accidentally destroyed in error.

14.0 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 prisoner into the study. The approval letter/document must clearly identify the protocol and all documents approved by the IRB/EC 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/EC reporting requirements for all adverse events, 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 nursing/site study coordination staff. Consent must be documented by the prisoner's dated signature on the participant information and consent form together with the dated signature of the person conducting the consent discussion.

If the prisoner is illiterate, an impartial witness should be present during the entire consent discussion. Once the discussion is complete, the prisoner 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.

If the prisoner is legally incompetent (i.e. mentally incapacitated) the written consent of a parent, guardian or legally authorised representative must be obtained.

A copy of the signed and dated participant information and consent form must be given to the person prior to study participation. The prisoner 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).

15.0 Confidentiality of data

15.1 Confidentiality of participant records

By signing the protocol signature page, the site Principal Investigator and site staff agree 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 prisoner agrees to these processes.

Prisoner confidentiality will be maintained at all times and no documents containing the prisoner'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 prisoner's medical records. If study documents need to be photocopied during the process of verifying case report form data, the prisoner will be identified by a unique code only; full names and other identifying information will be masked.

15.2 Confidentiality of study data

By signing the protocol signature page, the site Principal Investigator and site staff 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.

16.0 Governance

A Protocol Steering Committee will be established and will consist of the study investigator team, community representatives and representatives from Justice Health & Forensic Mental Health Network, NSW Health and Corrective Services NSW.

17.0 Financing and insurance

This research study is funded by a National Health and Medical Research Council Partnership Grant, Gilead Sciences Inc, and the University of New South Wales (UNSW). The study intervention/clinical trial supplies are provided by Gilead Sciences. The study is sponsored by the University of New South Wales (UNSW) and coordinated through the Kirby Institute for infection and immunity in society. The study is indemnified by the University of New South Wales. Compensation is available to prisoners in the event of study-related injury.

18.0 Quality Control (QC) and Quality Assurance (QA)

By signing this protocol, 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.

19.0 Publication Policy

Publication of data derived from this protocol will be supervised by the Protocol Steering Committee in accordance with the study Publications Policy. No other publication, either in writing or verbally, will be made before the definitive manuscript has been agreed upon and accepted for publication and without prior approval of the study principal investigators.

Proposals for additional projects or collaborations, likely to result in separate publications, will be reviewed by the Protocol Steering Committee for final determination. Investigators and members of the Protocol Steering Committee will be included as co-authors on additional publications provided the ICMJE (International Committee of Medical Journal Editors) guidelines are met.

All publications must be submitted to Gilead Sciences for review at least 30 days in advance of any submission to a journal or publication and 7 days in advance of any submission for a scientific meeting or conference.

List of References

1. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis. 2005; 5(9): 558-67.
2. Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horyniak D, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet. 2011; 378(9791): 571-83.
3. Degenhardt L, Mathers B, Vickerman P, Rhodes T, Latkin C, Hickman M. Prevention of HIV infection for people who inject drugs: why individual, structural, and combination approaches are needed. Lancet. 376(9737): 285-301.
4. Hagan H, Pouget ER, Des Jarlais DC. A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs. The Journal of infectious diseases. 2011; 204(1): 74-83.
5. Sacks-Davis R, Horyniak D, Grebely J, Hellard M. Behavioural interventions for preventing hepatitis C infection in people who inject drugs: A global systematic review. Int J Drug Policy. 2012; 23(3): 176-84.
6. Turner KM, Hutchinson S, Vickerman P, Hope V, Craine N, Palmateer N, et al. The impact of needle and syringe provision and opiate substitution therapy on the incidence of hepatitis C virus in injecting drug users: pooling of UK evidence. Addiction (Abingdon, England). 2011; 106(11): 1978-88.
7. Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Ann Intern Med. 2012; 156(4): 271-8.
8. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008; 48(2): 418-31.
9. Grebely J, Dore GJ. What is killing people with hepatitis C virus infection? Semin Liver Dis. 2011; 31(4): 331-9.
10. Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. Clin Infect Dis. 2009; 49(4): 561-73.
11. Aspinall E, Corson S, Doyle J, Grebely J, Hutchinson SJ, Dore GJ, et al. Peginterferon and ribavirin treatment for chronic hepatitis C virus in people who inject drugs: A systematic review and meta-analysis. Addiction (Abingdon, England). 2012; Under Review.
12. NCHECR. HIV/AIDS, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report: National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales; 2009.
13. Mehta SH, Genberg BL, Astemborski J, Kavasery R, Kirk GD, Vlahov D, et al. Limited uptake of hepatitis C treatment among injection drug users. J Community Health. 2008; 33(3): 126-33.
14. Grebely J, Raffa JD, Lai C, Krajden M, Kerr T, Fischer B, et al. Low uptake of treatment for hepatitis C virus infection in a large community-based study of inner city residents. J Viral Hepat. 2009; 16(5): 352-8.
15. Strathdee SA, Latka M, Campbell J, O'Driscoll PT, Golub ET, Kapadia F, et al. Factors associated with interest in initiating treatment for hepatitis C Virus (HCV) infection among young HCV-infected injection drug users. Clin Infect Dis. 2005; 40 Suppl 5: S304-12.
16. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011; 365(6): 493-505.
17. Durier N, Nguyen C, White LJ. Treatment of hepatitis C as prevention: a modeling case study in Vietnam. Plos One. 2012; 7(4): e34548.
18. Hellard ME, Jenkinson R, Higgs P, Stoove MA, Sacks-Davis R, Gold J, et al. Modelling antiviral treatment to prevent hepatitis C infection among people who inject drugs in Victoria, Australia. Med J Aust. 2012; 196(10): 638-41.
19. Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. Journal of hepatology. 2011; 54(6): 1137-44.
20. Martin NK, Vickerman P, Hickman M. Mathematical modelling of hepatitis C treatment for injecting drug users. Journal of theoretical biology. 2011; 274(1): 58-66.
21. Martin NK, Pitcher AB, Vickerman P, Vassall A, Hickman M. Optimal control of hepatitis C antiviral treatment programme delivery for prevention amongst a population of injecting drug users. Plos One. 2011; 6(8): e22309.

22. Matser A, Urbanus A, Geskus R, Kretzschmar M, Xiridou M, Buster M, et al. The effect of hepatitis C treatment and human immunodeficiency virus (HIV) co-infection on the disease burden of hepatitis C among injecting drug users in Amsterdam. Addiction (Abingdon, England). 2012; 107(3): 614-23.
23. Vickerman P, Martin N, Hickman M. Can Hepatitis C virus treatment be used as a prevention strategy? Additional model projections for Australia and elsewhere. Drug Alcohol Depend. 2011; 113(2-3): 83-5; discussion 6-7.
24. Zeiler I, Langlands T, Murray JM, Ritter A. Optimal targeting of Hepatitis C virus treatment among injecting drug users to those not enrolled in methadone maintenance programs. Drug Alcohol Depend. 2010; 110(3): 228-33.
25. Dore GJ. The changing therapeutic landscape for hepatitis C. Med J Aust. 2012; 196(10): 629-32.
26. Butler T, Milner L. The 2001 Inmate Health Survey. Sydney: NSW Corrections Health Service. ISBN: 0 7347 3560 X.; 2003.
27. Butler T, Boonwaat L, Hailstone S, Falconer T, Lems P, Ginley T, et al. The 2004 Australian prison entrants' blood-borne virus and risk behaviour survey. Aust NZ J Publ Heal. 2007; 31: 44-50.
28. Martire KA, Larney S. Inadequate data collection prevents health planning for released prisoners. Med J Australia. 2009; 191: 408-9.
29. National Prison Entrants' Bloodborne Virus and Risk Behaviour Survey Report: Kirby Institute; 2011.
30. Teutsch S, Luciani F, Scheuer N, McCredie L, Hosseiny P, Rawlinson W, et al. Incidence of primary hepatitis C infection and risk factors for transmission in an Australian prisoner cohort. BMC Public Health. 2010; 10: 633.
31. Luciani F, Teutsch S, Amin J, Topp L, Levy MH, Haber PS, et al. Hepatitis C incidence and risk behaviours in Australian prisoners: a prospective study. In Preparation.
32. Boonwaat L, Haber PS, Levy MH, Lloyd AR. Establishment of a successful assessment and treatment service for Australian prison inmates with chronic hepatitis C. Med J Aust. 2010; 192(9): 496-500.
33. 2009 NSW Inmate Health Survey: Key Findings Report: Justice Health; 2009.

Appendix 1: Abbreviations List

AE	Adverse event
AFP	Alpha-fetoprotein
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
Chronic HCV	Positive tests for HCV antibodies and HCV RNA for > 6 months and detectable HCV RNA at screening
eCRF	Electronic Case Report Form
EOT	End of Treatment (date of last dose of study drug)
ETR	End of Treatment Response, undetectable HCV RNA at EOT
EVR	Early Virological Response, undetectable HCV RNA OR a $\geq$2 log drop in HCV RNA at week 12 of treatment
FBC	Full Blood Count – haemoglobin, white blood cell, platelets, neutrophils
FT4	Free T4 (thyroxine)
GGT	Gamma Glutamyl Transpeptidase
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
Injection Drug use	Self reported injection drug use ever
IDUs	Injection Drug Users
INR	International Normalised Ratio
LFT	Liver Function Tests - albumin, total bilirubin, AST, ALT, GGT
PEG-IFN	Pegylated interferon
PR	Pulse rate
PT	Prothrombin time
RBC	Red Blood Cell
RBV	Ribavirin
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SOF/VEL	Sofosbuvir/Velpatasvir
SVR4	Sustained Virological Response, undetectable HCV RNA at 4 weeks post-end of treatment
SVR12	Sustained Virological Response, undetectable HCV RNA at 12 weeks post-end of treatment
SVR24	Sustained Virological Response, HCV RNA undetectable at 24 weeks post-end of treatment
TFT	Thyroid Function Tests – TSH, FT4,
TSH	Thyroid Stimulating Hormone
UEC	Urea, Electrolytes and Creatinine

Appendix 2: Modelling Estimates

We have modelled transmission and incarceration dynamics in the two proposed correctional centre settings (short vs. long term incarceration). The mathematical model and the associated assumptions are shown below. Incidence is calculated over a 6 month period, such that the final incidence is calculated over the final 6 months of the trial (months 18-24). In a medium security correctional centre of 270 prisoners (given a correctional centre entry baseline chronic HCV prevalence of 30% (HCV Ab+ of 40%), an incidence of 15 per 100 person-years and an incarceration duration of 9 months, Table 1), it is estimated that 81 people would need to be treated per year to achieve a 50% reduction in HCV incidence (162 people over two years).

Table 1. Modelling estimates of the necessary numbers of people treated per year to achieve a 50% reduction the incidence in HCV infection in a medium security correctional centre with varying incidence and incarceration duration.

Incidence among ever-injectors	Incarceration duration of 6 months	Incarceration duration of 9 months	Incarceration duration of 12 months
5 per 100 py	100	75	64
10 per 100 py	102	78	67
15 per 100 py	105	81	71
20 per 100py	106	84	75
25 per 100 py	109	87	79

In the maximum security correctional centre of 325 prisoners (given a correctional centre entry baseline chronic HCV prevalence of 26% (HCV Ab+ of 35%), an incidence of 15 per 100 person-years and an incarceration duration of 36 months, Table 2), it is estimated that 69 and 58 people would need to be treated in years 1 and 2 to achieve a 50% reduction in HCV incidence (127 people over two years). Overall, fewer treatments are needed in the maximum security correctional centre compared with the medium security correctional centre due to a lower HCV prevalence and lower turnover. Projections are also less sensitive to differences in incarceration duration as the study length is short in comparison.

Table 2. Modelling estimates of the necessary numbers of people treated per year to achieve a 50% reduction the incidence in HCV infection in a maximum security correctional centre with varying incidence and incarceration duration.

Incidence among ever-injectors	Incarceration duration of 24 months	Incarceration duration of 36 months	Incarceration duration of 48 months
5 per 100 py	53	50	50
10 per 100 py	59 (year 1) 55 (year 2)	59 (year 1) 58 (year 2)	62 (year 1), 59 (year 2)
15 per 100 py	66 (year 1) 56 (year 2)	69 (year 1) 58 (year2)	76 (year 1) 56 (year 2)

Mathematical model

To evaluate the impact of HCV antiviral treatment on HCV prevalence and incidence within prison, we construct a model of HCV treatment within prison, including dynamic HCV transmission among people who are currently injecting drugs while in prison. As the vast majority of HCV infections will be among people with a history of injecting, we make the simplifying assumption that all incoming HCV cases are among ever-injectors. Therefore, it is only necessary to explicitly model the ever-injector correctional centre sub-population (stratified into currently/not currently injecting in prison). To calculate HCV chronic prevalence among the whole correctional centre population, we divide the number of chronic infections among ever-injectors by the total correctional centre population size.

We track ever-injectors who are uninfected (X_j), chronically infected (C_j), on HCV antiviral treatment (T_j), and treatment failures (F_j). Additionally, the model is stratified by those who are not currently injecting in prison (j=0) and those who are current injecting in prison (j=1). The basic model schematic can be seen in **figure 1**.

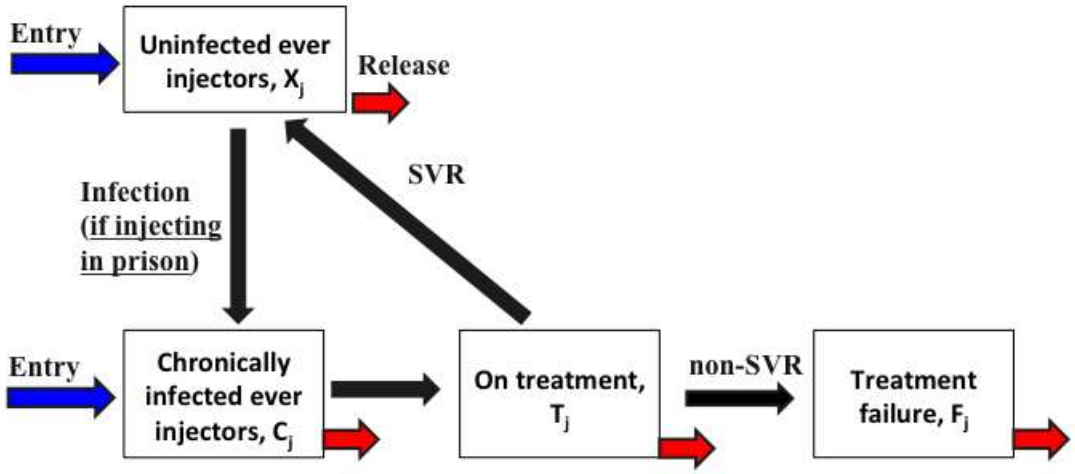

Figure 1. Model schematic. The model is stratified by those who are not currently injecting in prison (*j*=0) and those who are current injecting in prison (*j*=1).

Therefore, in the model, $X_j+C_j+T_j+F_j$ represents the total number of ever-injectors in prison, which is estimated by multiplying the total correctional centre size (Ω) by the proportion of prisoners who are ever injectors (Y)). Importantly, we do not use self-report data to determine the proportion of prisoners who are ever injectors (Y). Instead, Y is calculated by dividing the HCV chronic prevalence among correctional centre entrants (Ψ) by the HCV chronic prevalence among ever-injectors in the community.

New ever-injector prisoners enter the correctional centre at a rate (θ), a proportion of whom will inject in prison (ϕ), and the remainder of which (1-ϕ) who will not inject in prison. Of the new entrants, a proportion of those will be chronically infected with HCV (Ψ), and we assume the remainder (1-Ψ) are not chronically infected. We assume no entrants are currently on HCV treatment, or have previously been treated and failed treatment as treatment rates among injectors are low (<1%).

All those who are chronically infected with HCV (C_j) are eligible for treatment, at a rate Φ people per year. Treatments are split proportionally between those who are not currently injecting in prison (C_0) and those who are (C_1). Those who are on treatment remain on treatment for a duration (1/ω), after which a proportion (α) attain SVR and return to the uninfected compartment (X_j). After treatment, those who attain SVR and are currently injecting in prison are susceptible to HCV reinfection. The remainder who fail treatment (1-α) move to the treatment failure compartment where they remain chronically infected and cannot be retreated.

The model dynamically tracks within-prison transmission of HCV by assuming that uninfected injectors who report current injecting in prison (X_1) can become infected with a force of infection λ, which is related to HCV prevalence among currently injecting prisoners. A proportion (δ) spontaneously clear the acute infection, with the remainder (1-δ) progressing to chronic infection.

Finally, all prisoners can be released after an average duration of incarceration of 1/μ. For this simple model, we assume that the duration of incarceration does not vary by injecting status. We also assume that the all those who exit prison do so by release, and therefore death within prison is ignored as it is assumed to be negligible.

Therefore the full set of model equations are as follows:

$$\frac{dX_0}{dt} = \theta(1-\varphi)(1-\psi) + \alpha\omega T_0 - \mu X_0$$
$$\frac{dC_0}{dt} = \theta(1-\varphi)\psi - f(C_0) - \mu C_0$$
$$\frac{dT_0}{dt} = f(C_0) - \omega T_0 - \mu T_0$$

$$\frac{dF_0}{dt} = (1-\alpha)\omega T_0 - \mu F_0$$

$$\frac{dX_1}{dt} = \theta\varphi(1-\psi) - (1-\delta)\lambda_1 X_1 + \alpha\omega T_1 - \mu X_1$$

$$\frac{dC_1}{dt} = \theta\varphi\psi + (1-\delta)\lambda_1 X_1 - f(C_1) - \mu C_1$$

$$\frac{dT_1}{dt} = f(C_1) - \omega T_1 - \mu T_1$$

$$\frac{dF_1}{dt} = (1-\alpha)\omega T_1 - \mu F_1$$

The force of infection (λ_1) is defined by:

$$\lambda_1 = \pi \frac{C_1 + (1-\alpha)T_1 + F_1}{X_1 + C_1 + T_1 + F_1}$$

We therefore assume proportional mixing between the current injectors, and also that while on a treatment, the proportion of current injectors expected to fail treatment (1-α) are infectious, while the remainder expected to achieve SVR (α) are non-infectious. Here, π represents the infection rate.

As treatments are allocated proportionally between chronically infected prisoners who are currently and not currently injecting,

$$f(C_1) = \Phi \frac{C_1}{C_1 + C_0}$$

$$f(C_0) = \Phi \left(1 - \frac{C_1}{C_1 + C_0}\right)$$

where $f(C_j)=0$ if $C_j=0$.

Calculation of prison HCV chronic prevalence:
We calculate the prison HCV chronic prevalence by summing the number of chronic infections in our model and dividing by the total number of prisoners (including non-injectors). We assume that those who are on treatment will be included in the prevalence estimate, with the number expected to achieve SVR (αT_j) testing RNA negative during treatment due to the rapid reduction in viral loads on treatment. We therefore assume that the remainder ($(1-\alpha)*T_j$) will test RNA positive during treatment. Therefore, if Ω represents the total prison size.

$$Prison\ HCV\ chronic\ prevalence = \frac{C_0 + (1-\alpha)T_0 + F_0 + C_1 + (1-\alpha)T_1 + F_1}{\Omega}$$

Calculation of HCV incidence among uninfected ever-injectors:
We calculate the HCV incidence among uninfected ever-injectors over a 6 month period. The baseline incidence is calculated at model steady-state (prior to initiation of treatment), and the final incidence is calculated over the final 6 months of the trial (months 18-24).

$$HCV\ incidence = \frac{\sum(1-\delta)\lambda_1 X_1}{\sum(X_1 + X_0)}$$

Parameterization:
A table of the parameter values used can be found in **Table 1**.

Parameter	Symbol	Medium Security Correctional centre	Maximum Security Correctional centre

Total correctional centre size	Ω (used to calculate θ[a])	270	325
HCV chronic prevalence among all correctional centre entrants	Ψ	30%	26%
Average incarceration duration	$1/\mu_1$	0.5-1 years	2-4 years
HCV incidence among ever-injectors	Varied π to fit	5-25 per 100 py	5-15 per 100 py
Fraction of entrants with injecting history[b]	Y (used to calculate θ[a])	65%	57%
Fraction of ever-injectors reporting correctional centre injecting	ϕ	60%	60%
SVR	α	90%	90%
Treatment duration	52/ω	12 weeks	12 weeks
Proportion spontaneously clear acute infection	δ	25%	25%

Table 1. Model parameters. [a]We calculate θ to ensure a total correctional centre size of Ω, and therefore a total ever-injector correctional centre size of ΩY. Therefore, θ=μΩY. [b]Calculated by dividing the HCV chronic prevalence among correctional centre entrants (Ψ) by the HCV chronic prevalence among ever-injectors in the community (estimated at 46% (62% Ab+).

Appendix 3: Investigator agreement and signature page

between the UNSW and the site investigator(s) and site staff

Site Name:

Principal Investigator:

Co-investigators and Site Staff (please list, if applicable):

_____ _____

_____ _____

_____ _____

Study Title: **Surveillance and Treatment of Prisoners with Hepatitis C (SToP-C)**

A pilot study to assess the feasibility of HCV treatment as prevention with interferon-free Direct Acting Antivirals (DAAs) in the prison setting

Protocol Version Number: **6.0**

Protocol Version Date: **12 October 2016**

I/We agree to follow the procedures outlined in this protocol. I/We accept responsibility for the conduct of the research detailed in the proposal including all protocol-specific assessments, and I/We agree to abide by all decisions made by our Ethics Committee and Regulatory Agency. I/We agree to ensure the informed consent process is conducted with each participant in compliance with ICH GCP guidelines.

PRINCIPAL/RESPONSIBLE INVESTIGATOR
(signature and date)

_____

CO-INVESTIGATOR(S) / SITE STAFF
(signature(s) and date(s))

_____

UNSW REPRESENTATIVE

(signature and date)

_____

_____

Appendix 4: Qualitative Research Substudy

Rationale

Although the implementation of HCV treatment as prevention in correctional settings is well-grounded in evidence and the logic of attending to populations of high prevalence, the acceptability of such an innovation cannot be assumed in a conservative and challenging environment such as correctional centres. This qualitative research will assess acceptability of the SToP-C intervention among a range of important groups. Also, this component will examine perceptions of what should constitute a program of HCV prevention in correctional centres beyond the treatment as prevention paradigm.

Aim

To evaluate Prisoner and provider attitudes and barriers towards the provision of treatment of HCV infection using standard therapy as compared to DAA-based therapy in the correctional setting.

Specific research questions

1. What are the elements of a HCV prevention program in correctional centres as perceived by male and female prisoners, custodial officers, families of prisoners and stakeholders/advocates in the HCV, IDU and correctional sectors?
2. What is the acceptability of the STOP-C HCV treatment as prevention among prisoners (including those who agreed and did not agree to treatment), prisoner officers and families of NSW prisoners?
3. What is the experience of prisoners who undertake hepatitis C treatment in correctional centres?
4. What is the experience of stakeholders in conducting and observing the STOP-C project in NSW correctional centres?

Sample Size

Interviews will be conducted with:

- male and female, uninfected and infected, prisoners in correctional centres where treatment-as-prevention has not yet been commenced and where it has been initiated and (n=30);
- families of prisoners (unlinked to prisoners being interviewed) (n=10);
- custodial officers (n=10);
- correctional centre health staff (n=10);
- policy makers at local and state levels (n=10); and
- consumer advocates (n=5).

Participant Recruitment

Prisoners enrolled in the SToP-C study (at all correctional centres) will be invited to participate in a voluntary and confidential interview with a researcher, for an additional participant payment. Prisoners can indicate their interest in participating and an interview will be arranged.

Community organisations providing support programs for families of prisoners will distribute information about the study, including an invitation for family members to contact researchers to initiate participation. Custodial officers and Justice Health staff will be approached directly after approval by local senior Corrective Services and Justice Health managers. The SToP-C Steering Committee will identify organisations or individuals who undertake relevant activities in policy and advocacy who will be approached to participate by email.

Methods

Following informed consent, audio-recorded interviews will be conducted in a conversational style guided by an interview schedule. The recordings will be transcribed verbatim and cleaned to remove identifying information. Analysis will proceed using a mix of inductive and deductive processes - guided by interests

in the feasibility and acceptability of the treatment-as-prevention in the correctional setting, and exploring the socially and structurally mediated meanings of these opinions.

Interview topics:

1. Hepatitis C prevention in the correctional setting:

- Perceptions of current activities of HCV prevention in NSW correctional centres.
- Perceptions of what HCV prevention could include in the future.
- Perceptions of acceptability and feasibility of these activities (covers injecting risks as well as tattooing, piercing and fighting)
- Perceptions of the opinions of others.

2. Hepatitis C treatment in the correctional setting:
    - From what you've heard about hepatitis C treatment, how would you describe it?
    - How likely are you to consider hepatitis C treatment in prison? (relating to current treatments)
    - What are the factors influencing your decision? (include in prompts: individual level factors (how they feel about having hepatitis C; symptoms); family/social factors (want to be healthy for family and live longer life); system factors (access to treatment in prison)
    - What are the advantages of having treatment in prison?
    - What are the disadvantages of having treatment in prison?
    - Have you had discussions about hepatitis C with other prisoners? What are the general opinions of treatment?

3. New treatments for hepatitis C

- Explain possibility of new treatments
- Would you have a different decision about having new treatment versus the current treatment? Why?
- What are the advantages of having new treatment in the correctional setting?
- What are the disadvantages of having new treatment in the correctional setting?
- For prisoners who inject drugs - explain that new treatments might mean that people clear hepatitis C quickly, but that the risk of reinfection after treatment will remain
- We have heard that prisoners sometimes choose who they inject with on the basis of hepatitis C status. How do you think new treatments might impact on decisions about who you inject with?
- What would this new treatment change with regard to injecting in the correctional centre?
- What would not change?

4. SToP-C experiences

- Understanding of SToP-C trial
    - Can treatment have a role in prevention? [with follow-up probe]
- Acceptability of the trial including different response to different treatment scenarios
- Interest in participating if it was offered
- Perceptions of other prisoners' perceptions of the trial.
- Perceptions of organisational barriers to the trial
- Perceptions of family members' views of the trial.
- <u>For prisoners who did/did not consent to participate in trial</u>: factors that influenced their decisions.
- <u>For custodial officers and Justice Health staff</u>: how did/would the SToP-C trial impact on work and organisational issues including impact of different types of correctional centres

- For families: perceptions of extent of impact of HCV (and its treatment) on family life, and on prisoner.
- For stakeholders: perceptions of these risks/benefits of SToP-C trials to HCV advocacy.

Debriefing – for prisoners and families

- Ensure that participant understands that whether new treatments are available (or not) in their setting
- Ensure that participant understands that any risks should continue to be managed as best as possible

Appendix 5: Peer education sub-study

Rationale:
Despite application of a multi-pronged patient recruitment strategy, enrolment coverage remains sub-optimal. The potential benefits of peer education in increasing recruitment will be examined as a sub-study. This component will assess the acceptability of hepatitis C education delivered at a peer-to-peer level and impact on uptake of testing and treatment.

Aim:
To evaluate prisoner receptiveness to testing and treatment of HCV following the implementation of a peer education program.

Specific research questions:
1. How effective is peer education in improving uptake of testing and treatment of HCV?
2. How likely is peer education to perpetuate further knowledge transmission amongst other peers, who are not necessarily involved in the sub-study?

Sample size:
A total of 10 peer educators per centre will be recruited (n=40).

Participant recruitment

Inclusion criteria:
1. Prisoners are to be nominated by the inmate development committee and/or health services (recommendations from JH&FMHN staff and SToP-C study nurses), with overall approval from corrective services.
2. Prisoner to be incarcerated for a minimum of 6 months from the time recruitment as peer educator occurs.
3. Willingness to participate and become a peer educator, through voluntary signature of the informed consent form.

Exclusion criteria:
1. The prisoner, in the opinion of corrective services, is not regarded as being of good character.
2. Prisoners of a security classification which logistically impedes the ability to act as a peer educator

Methods
Peer educators will be consented by the SToP-C study nurses. The informed consent discussion with the peer educators will emphasize that they should ensure that no coercion is exercised during their education sessions with other inmates, as well as emphasizing that they should ensure that specific details of individual persons or events pertaining to injecting behaviours should not be disclosed to them (as any specific offence details that are disclosed carry an obligation for the researchers to report to the authorities). The selected peer educators will be trained to educate their peers using the 'Hep C & You' peer education booklet, which covers the following modules:
- Module One: Liver Health
- Module Two: Hep C and Testing
- Module Three: Hep C Treatment and Prevention

The booklet provides moderately detailed, but low health literacy information regarding hepatitis C, including modes of transmission, the different tests conducted for diagnosis, and more general information on liver health.
For this sub-study, data from the educators regarding their peer educational activities will be collected, including the following:
- The number of inmates approached for education;

- The most effective method of educational booklet distribution (i.e. in person, hosting larger educational sessions, distribution in the yards versus clinics);
- The overall thoughts on inmate receptiveness to peer education;
- The quality of education provided by SToP-C nurses in equipping them to act as a peer educator.

Prisoners will be administered a qualitative interview by the SToP-C nurses at approximately three-monthly intervals, following the implementation of the peer education sub study.

The impact of the peer education will be evaluated by data available through the SToP-C study by assessment of the following:

- Rates of HCV testing and treatment prior to implementation of peer education
- Rates of HCV testing and treatment following implementation of peer education

Peer educators will be supported through regular de-briefing and support sessions with the SToP-C research team.