CONFIDENTIAL

STUDY PROTOCOL

Evaluation of Simplified HCV Diagnostics in HIV/HCV Co-infected Patients in Myanmar (Simplified Monitoring Myanmar SM^2 study)

Investigators:	**Australia:** A/Prof Gail Matthews Dr Josh Hanson Professor Greg Dore Dr Tanya Applegate A/Prof Jason Grebely Prof Mark Boyd Kirby Institute, UNSW Australia, Sydney, Australia **Myanmar:** Dr Kyaw Swar Lin Specialist Hospital Mingaladon, Yangon, Myanmar Prof Mar Mar Kyi Insein General Hospital, Yangon, Myanmar Prof Sabai Phyu Specialist Hospital Waibargi, Yangon, Myanmar Dr Ne Myo Aung Insein General Hospital, Yangon, Myanmar Dr Pyo Pyae Nyein Specialist Hospital Mingaladon, Yangon, Myanmar Dr Myint Myint Yee Specialist Hospital Mingaladon, Yangon, Myanmar

CONFIDENTIAL

INVESTIGATOR AGREEMENT AND SIGNATURE PAGE

Protocol Number: 001
Protocol Title: Simplified Monitoring Myanmar SM^2
Coordinating Investigator: Matthews and Lin
Protocol Version and Date: Version 2.0, dated 31 May 2018

RESEARCHER AGREEMENT ANS SIGNATURE PAGE

This study will be conducted in accordance with the National Statement on Ethical Conduct Involving Humans, ICH GCP, the Declaration of Helsinki and any recommendations of the Human Research Ethics Committee who approved the conduct of the study. The study will be carried out in accordance with the study protocol.
All participant data will be completely and accurately recorded. Access to participant data, source documents, study progress and consent forms, will be granted to Kirby Institute study staff and inspection by auditors from regulatory authorities, if necessary.
I accept responsibility for the conduct of the research detailed in the above named protocol and I agree to abide by all decisions made by the Human Research Ethics Committee.

Signature: _____ **Date:** _____

SITE INVESTIGATOR AGREEMENT AND SIGNATURE PAGE

Principal Investigator at Site: _____

Study Site: _____

This study will be conducted in accordance with the National Statement on Ethical Conduct Involving Humans, ICH GCP, the Declaration of Helsinki and any recommendations of the Human Research Ethics Committee who approved the conduct of the study at this site. The study will be carried out in accordance with the study protocol.
All patient data will be completely and accurately recorded in the patient case record forms (CRF). Access to CRFs, source documents, study progress and consent forms, will be granted to Kirby Institute study staff and inspection by auditors from regulatory authorities, if necessary.
Before entering this study, all patients will give their written informed consent. The original signed consent forms will be retained by the principal investigator in the investigator study file at site.
I accept responsibility for the conduct of the research detailed in the above named protocol and I agree to abide by all decisions made by the Human Research Ethics Committee.

Signature: _____ **Date:** _____

PLEASE POST ORIGINAL TO THE KIRBY INSTITUTE. FILE A COPY IN THE SITE INVESTIGATOR FILE (SECTION 1.0)

TABLE OF CONTENTS

Title: Evaluation of Simplified HCV Diagnostics in HIV/HCV co-infected patients in Myanmar

1.0 Background/Rationale:

Recent developments in hepatitis C virus (HCV) therapeutics, notably the introduction of interferon-free directly acting antiviral (DAA) regimens, have revolutionised the treatment landscape providing the potential to scale up therapy across broad populations living with HCV, including those in low and middle income countries (LMIC). Although costly, increasing production of generic alternatives to pharma marketed supply, including generic versions of sofosbuvir and daclatasvir, mean that relatively cheap courses of DAA combinations can now be purchased by individuals and governments to facilitate access for affected communities.

The extremely high efficacy and low toxicity of these regimens have also revolutionised the potential approach to treatment monitoring. Rates of on-treatment virological suppression close to 100% mean that on-treatment virological monitoring is no longer required, simplifying HCV RNA testing requirements to two time-points, a pre-treatment and SVR12 HCV RNA qualification. Further, the incredibly low rate of adverse events (equivalent to placebo) and minimal treatment drop-out rates mean that toxicity or safety monitoring can also be reduced to a minimum. These changes have major implications for the delivery of therapy on a broad scale, especially in countries where resources are limited.

However, major challenges still remain, particularly around the simplification of diagnostic and testing methodology [1]. Currently, the HCV testing algorithm involves the detection of HCV antibodies to confirm exposure followed by HCV RNA or core antigen testing to detect active infection. This two-step process to confirm active infection requires multiple visits and results in a loss of patients diagnosed with HCV infection[2-5]. In addition to multiple visits, HCV RNA determination (qualitative or quantitative) requires the collection and preparation of plasma in a standardised laboratory, with resultant significant expense and complexity, providing a major barrier to testing in many situations. Point-of-care HCV testing using oral fluid and fingerstick capillary blood rapid diagnostic testing has been shown to increase testing and linkage to care [6-10] However, many currently available point-of-care tests only measure HCV antibodies, not HCV RNA. More recently the development of rapid point-of-care (POC) tests to enable HCV RNA detection in the clinic (e.g. Xpert® HCV Viral Load, Cepheid®) has shown potential for implementation[11,12]. Currently, the only two CE-marked point-of-care HCV RNA assays (the Xpert® HCV Viral Load, Cepheid and the Genedrive® HCV ID Kit, Genedrive) both require venepuncture, which is challenging in settings without access to phlebotomists or among people with poor venous access, including people who inject drugs [13]. Further

improvements to this technology have demonstrated HCV RNA can also be detected in fingerstick capillary blood (Grebely Lancet Gastro 2017, and Lamoury under review).

Methodology involving the collection and testing of dried blood spot (DBS) for HCV RNA and/or HCV core antigen has further potential for significantly upscaling testing by simplifying linkage from the clinic through to treatment and care. Although showing great promise these new technologies require validation against the current gold standard of plasma HCV RNA quantification, both in resource rich and resource limited settings.

Myanmar is one of the designated 91 LMIC able to purchase generic DAA therapy without challenging patent. Approximately 2,000 courses of generic sofosbuvir/daclatasvir have recently been obtained by the National Hepatitis Control Program to be allocated to HCV patients (HIV positive and negative) in an initial roll-out of therapy to 5 treatment sites including Specialist Hospital Mingaladon and Specialist Hospital Waibargi in Yangon in 2017. Following the initial roll-out, a further 4,000 courses are expected to become available in 2018-2019. Additionally, a collaborative project between USAIDS and Myanmar Liver Foundation is expected to supply 4,000 treatment courses of sofosbuvir/velpatasvir +/- ribavirin commencing 2018 over 5 years, of which 20% will be allocated to people with HIV co-infection.

Specialist Hospital Mingaladon is one of the largest HIV treatment hospitals in Myanmar with an estimated 8,000 HIV positive patients, the majority of whom are maintained on ART (first line TDF/3TC/EFV, alternatives AZT/3TC/EFV and ABC/3TC/EFV plus second line (ritonavir boosted lopinavir (LPV/r) or atazanavir (ATV/r)). Median CD4 count at ART initiation is approximately 230 cells/mm^3, with the majority of patients maintained on first line ART. Due to the lack of free treatment, HCV antibody testing was not carried out routinely until June 2016. Routine testing of newly recruited HIV patients and old cohorts were made after June 2016 when the National Hepatitis Control Program pledged to start free treatment. As of February 2018, more than 7000 patients were tested and 359 were HCV antibody positive (5%), of which about 50 were either dead or lost to follow up. The first round of HCV treatment started at Mingaladon Hospital in June 2017 and approximately 260 patients were treated to already warehoused patients with sofosbuvir and daclatasvir. For HCV RNA testing, plasma is collected at Mingaladon Hospital and the samples are sent on the same day to the National Health Laboratory to be tested using GeneXpert module 4.

National Hepatitis Control Program is trying to implement free HCV treatment centres in large cities throughout the country but HCV diagnosis done on plasma at central specialised laboratory is a limiting factor. Fingerstick testing and running on GeneXpert machine has the potential for point-of-care service, with result turn-around time of an hour, minimising patient

visits and dropouts. DBS is easier to collect and easier to be transported to the central laboratory with smaller sample volume and transportation restrictions.

Collection of DBS at the local site at time of patient review is highly feasible and will allow comparison of the performance of both cAg and HCV RNA in DBS against the local gold standard. The anticipated delivery from 2018 onwards of approximately 200 plus treatment courses of sofosbuvir/daclatasvir to HIV-HCV co-infected patients at Specialist Hospital Mingaladon, followed by additional sites and regimens including sofosbuvir/velpatasvir, provides an invaluable setting in which to evaluate a number of key concepts critical for widespread HCV diagnostic and treatment uptake in LMIC settings.

2.0 Hypotheses

- Simplified virological and safety monitoring during and following DAA therapy is an effective and safe management strategy in a resource limited setting
- Novel diagnostic methods for HCV detection including DBS collection and fingerstick capillary HCV RNA testing (GeneXpert, Cepheid) will perform in an equivalent manner to standard plasma HCV RNA methodology

3.0 Objectives

3.1 Primary objective

To evaluate the proportion of patients with undetectable HCV RNA at 12 weeks post-treatment (SVR12) following a course of DAA therapy delivered using a simplified schedule of safety and virological monitoring.

3.2 Secondary objectives

1) To evaluate acceptability and feasibility of DBS collection in Myanmar.
2) To evaluate concordance pre and post therapy between HCV RNA (fingerstick) and standard plasma HCV RNA detections.
3) To evaluate concordance pre and post therapy between HCV core antigen (DBS) and standard plasma HCV RNA detections.
4) To evaluate concordance pre and post therapy between HCV RNA (DBS) and standard plasma HCV RNA detections.
5) To evaluate patients' knowledge on HCV by using set-up questionnaire.
6) To understand HCV virus patterns in Myanmar through phylogenetic sequencing.
7) To enhance and develop laboratory and research capacity at Specialist Hospital Mingaladon (SHM), Specialist Hospital Waibargi (SHW) and Insein General Hospital (IGH).

4.0 Methodology

A total of 200 HIV HCV co-infected patients who visit out-patient department of SHM/SHW/IGH from 2018 onwards will be enrolled by simple random sampling.

In addition to the procedures for their usual medical care, each participant will complete a questionnaire and require blood sample collection (extra 5 ml) at baseline (fingerstick and venepuncture) and at SVR12 (fingerstick alone).

Proportion of participants achieving SVR will be calculated. Concordance between standard of care method and new DBS method will be evaluated. Analysis will be performed using STATA (version 14.0; Stata Corporation, College Station, TX).

4.1 Study Population

All HIV-HCV coinfected patients planned to commence DAA therapy at Specialist Hospital Mingaladon and Waibargi +/- other treatment sites during the time period of the study

4.2 Inclusion criteria

Subjects must meet all of the following inclusion criteria to be eligible to participate in this study.

1) Have voluntarily signed the informed consent form.
2) 18 years of age or older.
3) HCV antibody
4) HIV antibody positive

4.3 Exclusion criteria

Subjects who meet any of the exclusion criteria are not to be enrolled in this study.

1) Clinically significant illness (other than HCV) or any other major medical disorder that may interfere with the participant treatment, assessment or compliance with the protocol
2) Creatinine clearance (CL_{cr}) < 30 mL/min at screening
3) Pregnant or nursing female.
4) Use of prohibited concomitant medications.
5) Inability or unwillingness to provide informed consent or abide by the requirements of the study.

4.4 Study sites

- Specialist Hospital Mingaladon
- Specialist Hospital Waibargi
- +/- Insein General Hospital (if HCV treatment program is being rolled out to include that hospital)

4.5 Study duration

Two years, starting from the launch of second round of HCV treatment, probably June 2018. The majority of warehoused HCV-HIV co-infected patients were already treated in the first round. Assuming 5-8 new patients per month at each Specialist Hospital, two years will elapse to reach the sample size of 200.

4.6 Criteria for withdrawal of participants

Participants can withdraw their consent from the study at any time**.**

5.0 Study Design

The study is a prospective observational study evaluating treatment outcomes and diagnostic testing methodology in a cohort of HIV-HCV coinfected individuals undergoing standard DAA (initially SOF/DAC) treatment delivery in the hospital outpatient setting in Myanmar. Since this is an observational cohort there is no formal sample size calculation. All patients commencing DAA therapy who agree to be enrolled during the period of the study will be included.

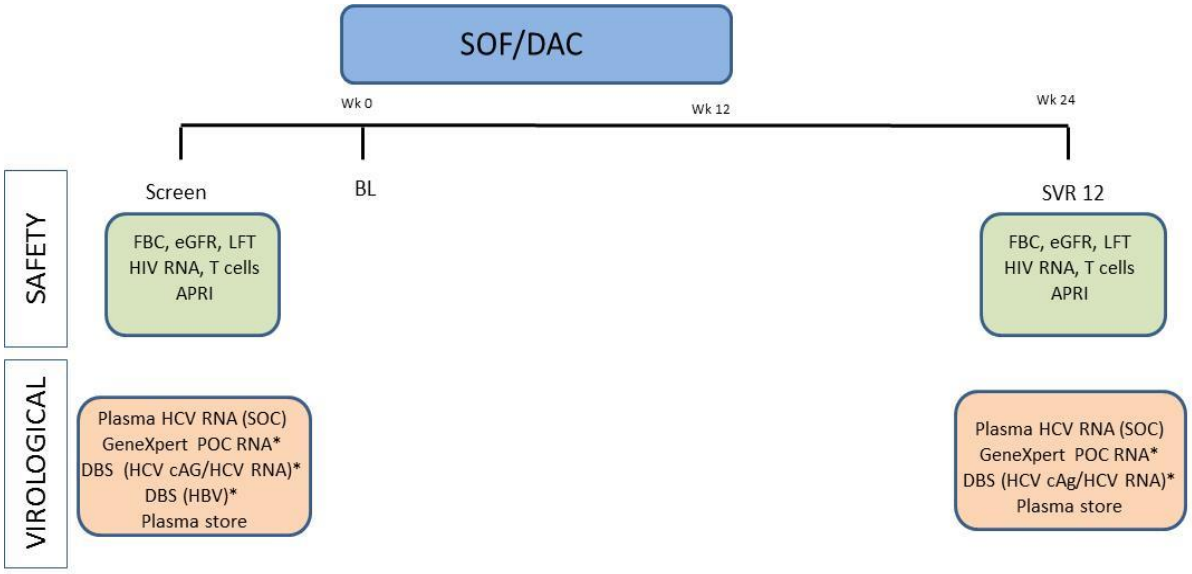

Fig 1. Schema for non-cirrhotic patients (treatment duration for decompensated cirrhotic patients 24 weeks) *via fingerstick testing

6.0 Study Procedures

6.1 Standard of care

Serological screening for viral hepatitis infection is now routinely done at both Specialist Hospitals Mingaladon and Waibargi. Those who tested positive for anti-HCV antibody by WHO pre-qualified test kit (SD Bioline) and who meet the treatment eligible criteria by "Simplified Treatment Guideline for HCV Infection, Myanmar"[14] (i.e. normal renal function, not pregnant, older than 18 years and not taking anti-TB drugs), will be given an appointment (first visit of HCV care). On that day, 10 ml of blood (6 ml for RNA, 1 ml for CBC and 3 ml for biochemistry) will be drawn for testing HCV RNA and other baseline tests. Three millilitres of plasma will be put in ice-box and sent to National Health Laboratory on the same day to test HCV RNA by GeneXpert 4 module machine. Baseline investigations are complete blood count (CBC), serum creatinine, ALT and ultrasound of the abdomen.

All patients will be given one week's appointment to enquire results (second visit of HCV care). Those with detectable HCV viral load (> 10 IU/ml) are offered DAA (Direct Acting Antivirals: sofosbuvir + dose adjusted daclatasvir). APRI score (ALT platelet ration index) is calculated. Significant fibrosis is defined as clinical cirrhosis with signs of chronic liver insufficiency and ascites, or fibrosis/cirrhosis on ultrasonography, or APRI score >2. The duration of treatment is 12 weeks for non-cirrhosis and 24 weeks for cirrhosis. Drugs are to be picked up monthly. Cure is determined by undetectable HCV RNA 12 weeks after completion of treatment.

6.2 Research

The study entry point to research will be the day when blood is collected by the program. Before blood collection, those who met the inclusion criteria will be interviewed by the investigator/research assistant and explained about the nature of research and invited to participate. After obtaining written informed consent, they will be asked to fill a demographic screening form (Behavioural Screening Questionnaire). Study staff will be available to assist participants to complete this questionnaire as required.

The investigator or research MO will collect information on HCV RNA, fibrosis state of the liver, CD4 counts, renal function and HCV medication (Pre-treatment Clinical Assessment).

Then 15 ml of venepuncture blood (10 ml for standard of care and extra 5 ml for research) and a single fingerstick blood will be collected (i) on GeneXpert cartridge (a variant cartridge that can run on fingerstick samples) and (ii) 4 or 5 blood drops will be put on dried blood spot cards, air-dried, transferred to -20^{o}C and batch shipped to VHCRP at Kirby Institute at the close of

the study. Five ml of whole blood will be immediately centrifuged at SHM laboratory to give rise to about 2.5 ml of plasma which is transferred to Common Research Laboratory of UM 2 on the same day to be stored there at -70^{o}C until batch-shipped to Kirby Institute, Australia. In VHCRP lab DBS will be analysed for HCV core antigen and HCV RNA by Abbott M2000/Architect machine.

All patients will undergo a second interview and clinical assessment 12 weeks after completion of HCV treatment. This includes all facts collected in the Pre-treatment clinical assessment plus major side effects the patients suffered (Post-treatment clinical assessment).

Participants will undergo the following testing as per the schedule of assessments

Table 1. Scheduled assessments

Assessment / Procedure	**Screening/baseline**	**Follow-up**
Study weeks	**-6 to 0**	**24 (SVR12)**
Informed consent, medical history, risk behaviour	x	
Liver function tests/ Full blood count/ eGFR	x	X
HIV RNA/ CD4 count	x	X
HCV-RNA testing (NHL) (Xpert®)	x	X
Finger stick capillary blood (Xpert®)[a]	x	X
Plasma store for HCV RNA[b] (Abbott)	x	X
Dried blood spot [c] (Abbott/Architect)	x	X

NHL = National Reference Laboratory

[a] Capillary blood collected by fingerstick and transferred to UM2 laboratory for HCV RNA testing using GeneXpert machine

[b] A single plasma store will be collected and stored at -70^{o}C for HCV RNA testing, plus future immunovirological research as allowed including HBV validation

[c] Fingerstick capillary blood air dried on filter paper and temporarily stored at -20^{o}C at Mingaladon, then sent to Kirby Institute for HCV and HBV testing and future immunovirological research

6.3 Virological testing

The following virological methodology will be employed:

1. Standard Plasma HCV RNA testing
   a. Myanmar
   A plasma sample will be taken pre-treatment initiation to confirm active HCV viremia before commencement of therapy. This sample will be sent to the National Health Laboratory in Yangon for testing as per the Myanmar HCV treatment guidelines. Current testing is with the GeneXpert technology (module 4).
   b. International
   A single HCV RNA plasma store will be collected and stored at -70^{o}C and batch shipped to VHCRP at Kirby Institute at the close of the study. The sample will be analysed for HCV RNA by Abbott M2000 RT machine, as an international standard to cross-validate DBS and local lab result.

2. Finger stick capillary blood sample *(research)*.
   A sample of whole blood will be collected via finger-stick for a HCV point of care test. This sample will be used to test HCV viral load via the Xpert® HCV Assay performed on the GeneXpert instrument system at the research laboratory. This test uses reverse transcriptase polymerase chain reaction (RT-PCR) and provides a measure of HCV RNA levels within 60 minutes.

3. Dried blood spot collection (DBS) for HCV core antigen and HCV RNA testing *(research)*.
   A finger-stick whole-blood sample will be collected for the dried blood spot sample collection using a (MiniCollect Safety Lancet; Greiner Bio-One, Monroe, Frickenhausen, German). Five spots (depending on available blood) of capillary whole-blood collected by finger-stick will be collected on dried blood spot cards, air-dried, transferred to -20^{o}C and batch shipped to VHCRP at Kirby Institute at the close of the study. In VHCRP lab DBS will be analysed for the presence of HCV, including HCV core antigen and HCV RNA.

Participants will not receive the results of any of the research samples as these are not accredited assays.

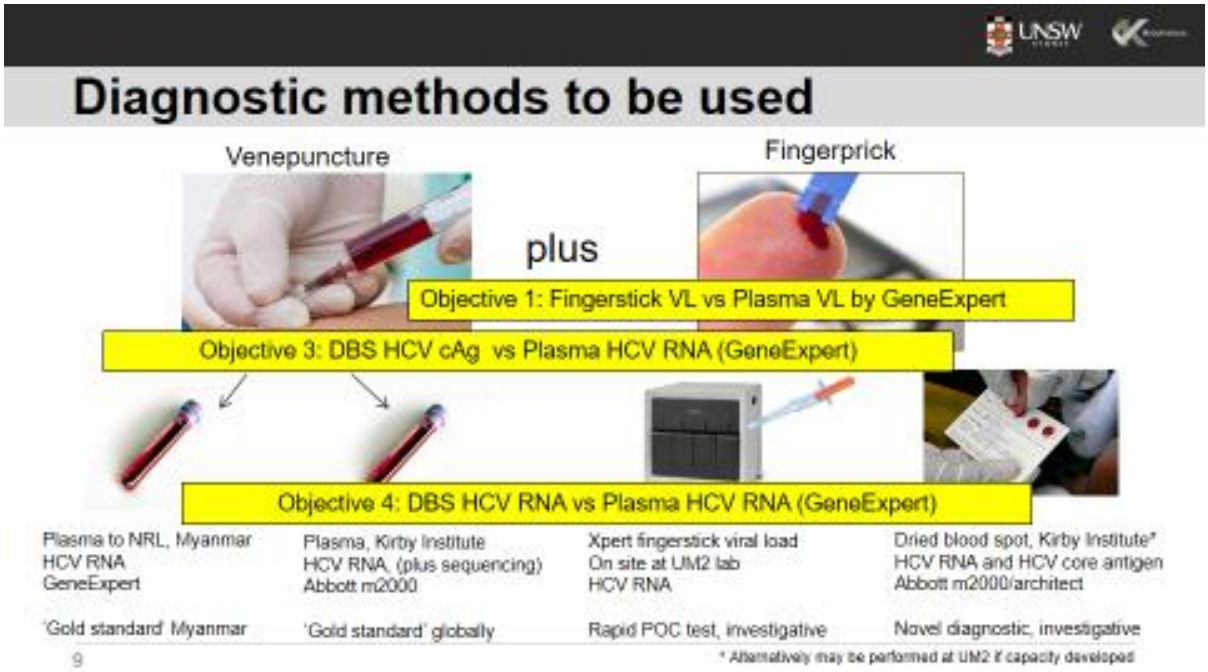

Fig 2. Diagnostic methods to be used

6.4 Methodology for Dried Blood Spot testing

HCV RNA testing using Abbott RealTime HCV Viral Load assay (Abbott Molecular, Illinois, United States) and HCV core antigen testing using the ARCHITECT HCV Ag will also be performed on dried blood spot as per manufacturer protocols. HBV will also be tested on dried blood spots as per manufacturers' protocols. Briefly, DBS spots will eluted in buffer, agitated by rotation for one hour at room temperature, centrifuged and analysed on the Abbott M2000RT Realtime PCR instrument, according to manufacturer's directions.

6.5 Sample transportation and storage

Some biological samples may eventually be transported to and stored at Kirby Institute. All staff that will be handling, packaging and/or transporting biological samples will be appropriately trained and will follow the correct sample collection and handling procedures.

6.6 Laboratory investigations

DBS samples and whole blood POC sample will be used for central lab HCV RNA testing. The DBS sample will be analysed to test for the presence of the hepatitis C virus, including HCV RNA. The sample will also be analysed to determine the genetic sequence of the HCV virus, which will then be assessed using phylogenetics, to compare it to other HCV sequences. The samples will be evaluated to explore potential transmission patterns among this population.

6.6.1 Whole blood in GeneXpert cartridge

GeneXpert machine to run on this sample is housed at Common Research Laboratory (CRL), University of Medicine 2. Whole blood obtained from fingerstick will be directly placed on GeneXpert cartridge, which will then be transported the CRL on the same day in ice-box. At the CRL, the sample will be tested on the same day or immediate next day. The samples will not be stored. The sample-containing cartridge will be discarded according to the laboratory's infection protocol.

6.6.2 Dried Blood Sample

Dried blood spot specimens will be collected by applying a few drops of blood, drawn by lancet from the finger, onto an absorbent filter paper. The blood is allowed to thoroughly saturate the paper and is air dried for a few hours. Specimens will be transferred into plastic bags with desiccant added to reduce humidity. These samples will be stored at -20^{o}C at CRL and batch-shipped to VHCRP at Kirby Institute at the close of the study. In VHCRP lab DBS will be analysed for the presence of HCV, including HCV core antigen and HCV RNA. The samples will not be stored at VHCRP. After analysis, the samples will be discarded.

6.6.3 Plasma

About 5 milliliters of venepunctured blood is centrifuged to give rise to 2.5 ml of plasma at site laboratory and transported to CRL in an ice-box on the same day. The samples will be stored at -70^{o}C in the freezer and batch-shipped to VHCRP laboratory in Sydney, Australia. The plasma samples will be stored for 2 years after completion of the study. If no continuation study arises, the samples will be destroyed. If a continuation study arises, the proposal will be submitted to ITERB of UOPH.

6.7 Questionnaires

All participants will complete a questionnaire at baseline and at SVR12. Questionnaires will be completed on paper or electronically on tablet. Study staff will be available to assist participants to complete this questionnaire as required.

a) The Behavioral Questionnaire

The behavioral survey will collect information on the following:

- Demographics
- Injecting and alcohol
- Drug treatment history
- Hepatitis C testing and treatment knowledge
- Quality of life

6.8 Clinical assessment

The clinic nurse or physician will assess the participant's medical history and known or likely liver disease related conditions. They will collect a sample of blood for routine clinical analysis. The pathology tests taken under the clinical assessment will not be regulated through this study. It is up to the study nurse or physician to decide on which tests are collected, based upon routine standard of care. These tests are part of normal standard of care practice.

7.0 Endpoints

7.1 *Primary endpoint*

- Proportion of patients achieving SVR 12 (HCV RNA < LLD at least 12 weeks post therapy completion)

7.2 *Secondary endpoints*

- Sensitivity and specificity of HCV RNA on GeneXpert machine using capillary blood collected via fingerstick compared to standard HCV RNA plasma tests
- Sensitivity and specificity of HCV RNA on DBS compared to standard HCV RNA plasma tests
- Sensitivity and specificity of HCV core antigen on DBS compared to standard HCV RNA plasma tests
- Proportion of patients identified with active HCV viremia at screening
- Change in HIV RNA/T cell count pre and post therapy
- Change in liver function tests and APRI score pre and post therapy
- Knowledge of the patients on HCV testing and treatment

7.3 *Sample size*

The sensitivity and specificity of the Abbott RealTime HCV assay on dried blood spot samples will be compared with the Abbott RealTime HCV assay on plasma samples collected via venepuncture. Assuming an SVR of 95%, (n=100, one sample at BL and SVR12, total n=200), a sensitivity and specificity of 95%, 200 samples would provide a 95% confidence interval of 89-98% for the estimates of sensitivity and specificity. Assuming an SVR of 95%, (n=150, one sample at BL and SVR12, total n=300), a sensitivity and specificity of 95%, 300 samples would provide a 95% confidence interval of 90-98% for the estimates of sensitivity and specificity. Assuming an SVR of 95%, (n=200, one sample at BL and SVR12, total n=400), a sensitivity and specificity of 95%, 400 samples would provide a 95% confidence interval of 91-98% for the estimates of sensitivity and specificity.

The sample size for the study is n=200 patients (n=400 samples) to provide a sensitivity/specificity of 95% with a 95% CI of 91-98%.

7.4 Statistical methodology

Descriptive analyses will be performed to characterise the study population including median (interquartile range) or mean (SD). Patient population will be described by age, sexual orientation, education, income, liver disease stage (categorised by APRI), drug and alcohol use, daily functioning and HIV parameters as well as HCV related parameters including HCV genotype and viral load. Continuous variables will be summarised by either mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate.

Factors associated with knowledge of liver disease will be assessed using logistic regression analyses. Variables hypothesized to be associated with HCV knowledge to be assessed in unadjusted analyses will include: sex, age, education, accommodation, employment, social functioning, injecting drug use, alcohol use and HCV infection status. All variables with $p<0.20$ in bivariate analysis will be considered in multivariate logistic regression models using a backwards stepwise approach sequentially eliminated subject to the result of a likelihood ratio test. Statistically significant differences will be assessed at $p<0.05$ (two-sided p-values).

Proportion of participants achieving SVR will be calculated. SVR12 will be defined as HCV RNA target not detected (TND) or target detected, not quantifiable (TD, nq) at post-treatment week 12. For the efficacy endpoint, means and proportions with two-sided 95% confidence intervals (CI) will be determined. Categorical data will be analysed using the Chi squared or Fisher's exact test. Continuous variables will be analysed using the t-test or the Mann-Whitney U test, as appropriate.

Logistic regression analysis will be used to identify factors associated with SVR. Potential predictors will be determined *a priori* and will include age, gender, liver disease stage (categorised by APRI), drug use and alcohol use, CD4 count and HIV RNA.

The multivariate models will be determined using a backwards stepwise approach, considering factors that were significant at the 0.2 level in univariate analysis. The final models will include factors that remain significant at the 0.05 level. All statistical tests will be two-sided with a significance level of 0.05. Analysis will be performed using STATA (version 14.0; Stata Corporation, College Station, TX).

8.0 Data Collection

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

All data collected will be entered into an electronic tablet or paper case report form. This will be managed by the data team at The Kirby Institute. Electronic data are on a password protected computer and data is stored on a secure server, which is backed up daily. Permission to access the dataset is only provided to individuals who are responsible for the data entry, upon completion of appropriate training from Kirby Institute staff. All required data collected must be complete, accurate and recorded in a timely manner by the site staff. The study questionnaires may act as the source document for the following study variables;

- Participant self-administered questionnaires
- Demographics

It is not acceptable for the study forms to be the only record of the participation in the study and the participant clinical data should also be recorded in the case notes.

The investigator and the institution where the study will be conducted will permit trial-related monitoring, audits and ethics committee review by providing direct access to the case notes.

The investigator is responsible for retaining all essential documents listed in ICH-GCP guideline. These should be organised in a comprehensive filing system that is accessible to study and other relevant personnel.

The investigator must retain all study documentation for 3 years following completion of the study. The investigator is responsible for ensuring that study records are not accidentally destroyed.

9.0 Recording and Reporting Adverse Events (AEs)

This is an interventional cohort study and no treatments are being administered as part of the study. Therefore, adverse events will not be collected. A history of any serious adverse event (death, pregnancy, hospitalisation, life threatening illness, congenital anomaly) will be collected at SVR12 time-point but is not required to be reported in real time.

10.0 Ethical Consideration

10.1 Patient recruitment

All HIV/HCV co-infected patients are recruited and treated as standard of care. They have equal chance to receive treatment. Whether they take part in the study or not, they will have free HCV treatment. Their participation in this research is entirely voluntary. Whether they choose to participate or not, all the services they receive will continue and nothing will change. They may change their mind later and stop participating even if they agreed earlier.

10.2 Risks and discomfort

The collection of blood via the finger prick method may be uncomfortable, but rarely results in any significant problem. The site of the piercing may be tender following the procedure. Collection of additional 4 ml of blood will not affect the patient's health.

10.3 Benefits

There is no guarantee that they will receive personal benefit from taking part in this study. However, their participation may provide valuable information to improve the management of people with hepatitis C in the future.

10.4 Incentives

The patients will not be given any other money or gifts to take part in this research.

10.5. Ethics Committee approval

The study has been reviewed and approved by the Human Research Ethics Committee of University of New South Wales and the Institutional Technical and Ethical Review Board of University of Public Health (Myanmar).

This study will be conducted in accordance with the ethical principles laid out in the Declaration of Helsinki (1996) and the National Statement on Ethical Conduct in Research Involving Humans.

11.0 Confidentiality of Data

Data confidentiality will be maintained at all times and no documents containing any identifying information will be made publicly available.

By signing of the protocol, the investigator agrees that the sponsor or their representative, HREC committee or regulatory authorities may consult and/or copy study documents to verify information in the cohort database. By signing of the consent form the participant agrees to this process. Participant confidentiality will be maintained at all times. Each participant will be assigned a unique participant identification number at enrolment comprising four letters of their alias, along with their date of birth.

All documents will be filed and stored separately at the respective sites, in a lockable cupboard, accessible by the site investigator only. If study documents need to be photocopied during the process of verifying case record form data, the participant will be identified by their unique study ID number. Full names will not be recorded.

Participant confidentiality is maintained at all times throughout this study. Participant data will be stored on a password protected EDC system, which is only accessed by authorised members of the research team. All data entered into this database are de-identified. Data will be kept in a secure location for a minimum of 7 years.

12.0 Financing

The study is being sponsored by Kirby Institute, UNSW Australia.

13.0 Publication Policy

Publication of data derived from this protocol will be supervised by the Protocol Steering Committee. No other publication, either in writing or verbally, will be made without prior approval of the Protocol Steering Committee.

REFERENCES

1. Ishizaki A, Bouscaillou J, Luhmann N, et al. Survey of programmatic experiences and challenges in delivery of hepatitis B and C testing in low- and middle-income countries. *BMC Infect Dis* 2017; **17**(Suppl 1): 696.
2. Yehia BR, Schranz AJ, Umscheid CA, Lo Re V, 3rd. The treatment cascade for chronic hepatitis C virus infection in the United States: a systematic review and meta-analysis. *PLoS One* 2014; **9**(7): e101554.
3. Snow K, Scott N, Clothier HJ, MacLachlan JH, Cowie B. Limited provision of diagnostic services to Victorians living with hepatitis C antibodies, 2001-2012: a multi-level modelling analysis. *Aust N Z J Public Health* 2016.
4. Mera J, Vellozzi C, Hariri S, et al. Identification and Clinical Management of Persons with Chronic Hepatitis C Virus Infection - Cherokee Nation, 2012-2015. *MMWR Morbidity and mortality weekly report* 2016; **65**(18): 461-6.
5. Janjua NZ, Kuo M, Yu A, et al. The Population Level Cascade of Care for Hepatitis C in British Columbia, Canada: The BC Hepatitis Testers Cohort (BC-HTC). *EBioMedicine* 2016; **12**: 189-95.
6. Bottero J, Boyd A, Gozlan J, et al. Simultaneous Human Immunodeficiency Virus-Hepatitis B-Hepatitis C Point-of-Care Tests Improve Outcomes in Linkage-to-Care: Results of a Randomized Control Trial in Persons Without Healthcare Coverage. *Open Forum Infect Dis* 2015; **2**(4): ofv162.
7. Coats JT, Dillon JF. The effect of introducing point-of-care or dried blood spot analysis on the uptake of hepatitis C virus testing in high-risk populations: A systematic review of the literature. *The International journal on drug policy* 2015; **26**(11): 1050-5.
8. Morano JP, Zelenev A, Lombard A, Marcus R, Gibson BA, Altice FL. Strategies for hepatitis C testing and linkage to care for vulnerable populations: point-of-care and standard HCV testing in a mobile medical clinic. *J Community Health* 2014; **39**(5): 922-34.
9. McAllister G, Innes H, McLeod A, et al. Uptake of hepatitis C specialist services and treatment following diagnosis by dried blood spot in Scotland. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology* 2014; **61**(3): 359-64.
10. Shivkumar S, Peeling R, Jafari Y, Joseph L, Pant Pai N. Accuracy of rapid and point-of-care screening tests for hepatitis C: a systematic review and meta-analysis. *Annals of internal medicine* 2012; **157**(8): 558-66.
11. Gupta E, Agarwala P, Kumar G, Maiwall R, Sarin SK. Point -of -care testing (POCT) in molecular diagnostics: Performance evaluation of GeneXpert HCV RNA test in diagnosing and monitoring of HCV infection. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology* 2017; **88**: 46-51.
12. McHugh MP, Wu AHB, Chevaliez S, Pawlotsky JM, Hallin M, Templeton KE. Multicenter Evaluation of the Cepheid Xpert Hepatitis C Virus Viral Load Assay. *J Clin Microbiol* 2017; **55**(5): 1550-6.
13. Day CA, White B, Thein HH, et al. Experience of hepatitis C testing among injecting drug users in Sydney, Australia. *AIDS care* 2008; **20**(1): 116-23.
14. Simplified Treatment Guideline for HCV Infection. First edition. February 2017. Ministry of Health and Sports