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# Towards HCV elimination among people who inject drugs in Hai Phong, Vietnam: study protocol for an effectiveness-implementation trial evaluating an integrated model of HCV care (DRIVE-C: DRug use & Infections in ViEtnam–hepatitis C)

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## ABSTRACT

**Introduction** In Vietnam, people who inject drugs (PWID), who are the major population infected by hepatitis C virus (HCV), remain largely undiagnosed and unlinked to HCV prevention and care despite recommended universal hepatitis C treatment. The data on the outcomes of HCV treatment among PWID also remain limited in resource-limited settings. The DRug use & Infections in ViEtnam–hepatitis C (DRIVE-C) study examines the effectiveness of a model of hepatitis C screening and integrated care targeting PWID that largely uses community-based organisations (CBO) in Hai Phong, Vietnam. In a wider perspective, this model may have the potential to eliminate HCV among PWID in this city.

**Methods and analysis** The model of care comprises large community-based mass screening, simplified treatment with direct-acting antivirals (DAAs) and major involvement of CBO for PWID reaching out, linkage to care, treatment adherence and prevention of reinfection. The effectiveness of DAA care strategy among PWID, the potential obstacles to widespread implementation and its impact at population level will be assessed. A cost-effectiveness analysis is planned to further inform policy-makers. The enrolment target is 1050 PWID, recruited from the DRIVE study in Hai Phong. After initiation of pan-genotypic treatment consisting of sofosbuvir and daclatasvir administrated for 12 weeks, with ribavirin added in cases of cirrhosis, participants are followed-up for 48 weeks. The primary outcome is the proportion of patients with sustained virological response at week 48, that will be compared with a theoretical expected rate of 70%.

**Ethics and dissemination** The study was approved by Haiphong University of Medicine and Pharmacy's Ethics Review Board and the Vietnamese Ministry of Health. The sponsor and the investigators are committed to conducting this study in accordance with ethics principles contained in the World Medical Association's Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects). Informed consent is obtained before study enrolment. The data are anonymised and stored in a secure database. The study is ongoing. Results will be presented at international conferences and submitted to international peer-review journals.

**Trial registration number** NCT03537196.

## Strengths and limitations of this study

- This is the first research evaluating the efficacy of a simplified hepatitis C virus (HCV) care model targeting people who inject drugs (PWID) in Vietnam.
- This study relies on a strong involvement of community-based organisations at all stages of the care process.
- Patient care is carried out within public hospitals.
- Study results will provide policy-makers with key data for scaling-up HCV care to eliminate HCV transmission among PWID.
- The current high price of direct-acting antivirals in Vietnam could jeopardise widespread access to treatment.

## INTRODUCTION

Treatment of hepatitis C was recently revolutionised with the development of direct-acting antivirals (DAAs).[1] Cure rate over 90%

can be achieved with shortened treatment duration (8–12 weeks) for almost all individuals with hepatitis C.[2] This progress opens a new era in which virtually all infected individuals can be cured if they are widely screened and have access to therapy. Hepatitis C elimination has been incorporated in the 2030 agenda of the WHO, which has set up ambitious targets as reducing new hepatitis C virus (HCV) infections by 80%, the number of HCV-related deaths by 65%, increasing hepatitis C diagnoses from 20% to 90% and eligible people receiving HCV treatment from <5% to 80%.[3]

However, more than 80% of the hepatitis C burden worldwide is in low-income and middle-income countries (LMIC), where access to diagnosis and treatment is limited.[4] Furthermore, people who inject drugs (PWID) are a major population affected by HCV with an estimated prevalence of approximately 60%–80%.[5] WHO's objectives will not be achieved without implementing simplified and cost-effective strategies targeting key populations, in particular PWID in LMIC. While high coverage of medication-assisted treatment (MAT) and needle/syringe exchange programmes alone cannot markedly reduce HCV transmission to low levels (unlike for HIV), new DAAs achieving high cure rate have such a potential impact.[6]

In Vietnam, around 1 million individuals are infected with HCV, and genotypes 1 and 6 represent almost 95% of hepatitis C infections.[7–9] For the last few years, the strong mobilisation of civil society has been crucial to recognising hepatitis C as a major public health issue, and to advocating for access to treatment. Although diagnosis, treatment, including DAAs since 2018, and monitoring costs are covered partially by the national social health insurance, the remaining cost is still too high for the most vulnerable patients, including PWID. In addition, limited access to HCV genotyping represents a major obstacle for scaling-up HCV treatment.

HCV prevalence ranges from 46% to 87% among PWID in Vietnam.[10–14] In 2008, local authorities piloted a new strategy policy for PWID based on access to MAT, universal antiretroviral treatment (ART) for HIV-infected PWID and a network of community-based organisations (CBO) to deliver harm reduction and distribute free syringes. Unlike HIV prevalence that has been reduced to 30% among PWID, the HCV epidemic is still very dynamic. In the DRIVE-IN (DRug use and Infections in ViEtnam - INitial phase) study (NCT02573948) conducted in 2014–2015 among PWID in Hai Phong,[15 16] HCV seroprevalence was 66%, 91% of HIV-infected participants were coinfected with HCV and HCV incidence was 18.8/100 person-years (95% CI: 11.2 to 29.8).[17]

### Drive program in Hai Phong

The city of Hai Phong, with about 9000 PWID out of a population of 2 million inhabitants, has a past HIV epidemic driven by heroin injection. HIV prevalence among PWID there peaked at 60% in 2006.[18] Our research group has been working in the field of drug use and HIV/HCV infection for the past 6 years in Hai Phong. After the successful implementation of the feasibility study DRIVE-IN, the DRIVE consortium designed an innovative strategy, aiming at 'ending the HIV epidemic among PWID'. In the DRIVE study (NCT03526939), the intervention strategy includes (1) a mass screening tool (3 repeated large-scale respondent-driven sampling (RDS) surveys over 2 years) to identify HIV-infected PWID in the community, (2) linkage to HIV care (to achieve viral suppression) by strong peer support and (3) improvement of harm reduction coverage by assisting actively injecting PWID to access MAT at existing centres and to reduce unsafe injection practices. In addition to the 3 RDS surveys, 2 cohorts were implemented, with follow-up (FU) visits at study sites every 6 months: (1) among HIV positive to monitor the intervention implementation and identify potential issues in the cascade of care and (2) among HIV negative to monitor HIV incidence and risk factors. The third RDS survey (DRIVE RDS3) was launched in October 2018.

### Research hypothesis

The DRIVE study offers a unique opportunity to extend interventions to hepatitis C. We hypothesise that a simplified model addressing all the following challenges could lead, if scaled up, to the elimination of HCV among PWID in Hai Phong:

- Identification of PWID with hepatitis C: to date only HIV-infected PWID registered in HIV outpatient clinics or PWID registered in methadone treatment centres have access to HCV screening with serology testing. HCV RNA is not routinely available.
- Improving health-seeking behaviours and referral to HCV care: PWID often have poor linkage with healthcare system, including fear or experience of stigmatisation, lack of self-esteem, limited access to health insurance and marginalisation.
- Setting-up a model of HCV care integrated in the local healthcare system: authorities will not launch specific HCV infection programmes but rather will integrate HCV care and treatment within existing infectious diseases or hepatology departments of health facilities.
- Optimised and tailored support for treatment adherence: some PWID present characteristics that may hamper medicine adherence (psychiatric disorders and marginalisation).
- Prevention of HCV reinfection after cure, which is crucial in a context of high HCV incidence: specific harm reduction and counselling activities, other than those for HIV, need to be elaborated.

## METHODS AND ANALYSIS

### Objectives

The primary objective of DRug use & Infections in ViEtnam–hepatitis C (DRIVE-C) is to assess the effectiveness of the proposed model of hepatitis C community-based screening and integrated care targeting PWID in Hai Phong, Vietnam.

Secondary objectives include: to assess all steps of the hepatitis C cascade of care; to assess the occurrence of adverse events and drug-related side effects; to evaluate adherence to HCV treatment; to determine factors associated with treatment failure; to estimate the reinfection rate at the end of the study; to identify risk factors for HCV reinfection and to project the impact and cost effectiveness of the implemented HCV treatment intervention.

## Outcome measures

The primary endpoint is the proportion of all patients in success of the model of care, defined by HCV RNA <10 IU/mL at the end of the study (week 48 visit).

What will be considered as failures: (1) detectable HCV RNA at "sustained virological response at post-treatment week 12" (SVR12) visit or at the end of study visit (HCV RNA ≥10 IU/mL), (2) missing HCV RNA result at the end of study visit, (3) HCV treatment not initiated within 1 year of HCV screening, (4) permanent discontinuation of DAAs, (5) death and (6) discontinuation of the study due to loss to FU or transfer out.

Secondary endpoints include the following:

- Evaluation of the HCV cascade of care, among all those with hepatitis C infection.
- Reinfection rate defined by HCV RNA ≥10 IU/mL at the end of the study among cured participants (HCV RNA <10 IU/mL at the SVR12 visit).
- Mortality rate among all participants.
- Frequency, type and time to grade 3 or 4, adverse clinical or biological events.
- Frequency, type and time to drug-related clinical or biological adverse reactions of grade 3 or 4 or leading to treatment interruption.
- Adherence assessed by self-questionnaire on DAA drug intake and drug accountability for DAAs.
- Factors associated with HCV treatment failure or HCV reinfection.
- Effect of the HCV treatment intervention on HCV infections and disability-adjusted life years (DALYs) averted, quality-adjusted life years (QALYs) saved, HCV incidence and prevalence as projected by the model under various scenarios.
- Incremental cost-effectiveness ratio (ICER).

## Study design

Because the aim of this research is to demonstrate how known effective treatment can be used in the Vietnamese context, we will conduct an effectiveness-implementation hybrid study type 1.[19] In addition, a modelling exercise to assess the impact of the intervention at the population level and a cost-effectiveness analysis to further inform policy-makers are included in the study.

The strategy of the model includes:

- Mass detection of hepatitis C infection among PWID, through a large community-based RDS survey.
- Community-based support to improve referral to specific care for those identified with hepatitis C infection.
- HCV care delivery integrated within the existing health system, with a simplified treatment protocol based on a combination of DAAs and considering PWID factors, such as frequent HIV co-infection and methadone treatment.
- Optimised treatment adherence through a combination of healthcare therapeutic education and CBO support.
- Increase in harm reduction activities to encompass HCV transmission risk and to prevent HCV reinfection.

Patients will be followed for 48 weeks after initiating HCV treatment.

## Study population

Participants enrolled are PWID who (1) either participated in the DRIVE RDS3 survey or have been enrolled in the DRIVE HIV-positive or HIV-negative cohort and performed an FU visit after RDS3, (2) have a hepatitis C infection defined by a positive HCV RNA at the time of screening and (3) sign the informed consent form.

All DRIVE participants were enrolled through RDS surveys and were active PWID, defined by a positive urine test result for heroin and recent injection marks, at the time of enrolment in DRIVE. At the time of enrolment in DRIVE-C, some of them may no longer inject drugs.

Non-inclusion criteria include: severe associated diseases requiring specific treatment; any condition which might compromise the safety of the patient by participating in the study; previous history of DAA use; contraindication to sofosbuvir or daclatasvir; for women of childbearing potential: pregnancy, breastfeeding or refusal to use a contraceptive method; renal failure with creatinine clearance ≤30 mL/min; being deprived of freedom by a judicial or administrative decision; planning to move out of Hai Phong in the next 12 months and being unable to understand the study.

## Study schedule

The total duration of the study will be 3 years, including 6 months of preparation, 1 year for enrolling and starting HCV treatment for all participants, 1 year of FU for each participant, and 6 months of data analysis.

## Study settings

Hepatitis C screening takes place in two DRIVE study sites run by CBO. Enrolment into DRIVE-C and FU are conducted in hepatitis clinics integrated within the departments of infectious and tropical diseases of three geographically distributed hospitals throughout the city (Viet Tiep Hospital, Kien An Hospital and Thuy Nguyen Hospital), representing both district and provincial level care settings.

## Implementation

### Screening

During DRIVE RDS surveys and cohort FU visits, participants are tested for HCV antibodies using rapid diagnostic test (SD Bioline) at the study community sites. At

the time of DRIVE RDS3 survey or a DRIVE cohort FU visit, participants (1) known to have an HCV seropositive result from a previous DRIVE visit or (2) newly screened HCV seropositive at that visit are informed of the nested research programme on hepatitis C infection (DRIVE-C). On participant's agreement, a blood sample is sent to a centralised laboratory, where the diagnosis of chronic hepatitis C is done using the GeneXpert System (Xpert HCV Viral Load test from Cepheid). Result is provided within 10 days.

Participants with hepatitis C infection proven by positive HCV RNA (≥10 IU/mL) are proposed to enrol in DRIVE-C. If interested, they will be contacted by CBO members to schedule an appointment at one of the three hepatitis clinics.

### Enrolment and FU

At the pre-inclusion visit, the physician checks that the participant fulfils the inclusion criteria and does not meet any of the non-inclusion criteria, then proceeds to the informed consent process. After consent obtention, clinical, laboratory and imaging assessments are performed. Liver assessment is based on the calculation of aspartate transaminase (AST) to Platelet Ratio Index score, abdominal ultrasound and fasting liver stiffness measurement with Fibroscan (Echosens). ART initiation and/or hepatitis B virus (HBV) treatment initiation are prescribed first when necessary. For those who are not already receiving methadone maintenance treatment (MMT), MMT initiation is strongly recommended.

The patient is successfully enrolled if all criteria are confirmed at the inclusion visit, planned as far as possible not later than 2 weeks after the pre-inclusion visit. After DAA initiation at inclusion visit, participants will undergo seven FU visits until the end of study (table 1 and figure 1). They shall include clinical examination, biological testing, drug dispensation, therapeutic education, assessment of adherence, referral to appropriate care in case of an ongoing adverse event, HCV-related counselling session focusing on reinfection after the end of treatment, administration of questionnaires and blood collection for sample repository.

End of treatment visit is performed 12 weeks or 24 weeks after treatment initiation according to its duration.

SVR12 visit and end of study visit are performed 12 weeks after the end of treatment and 48 weeks after treatment initiation, respectively, and include both HCV RNA testing and HCV genotyping in case of detectable HCV RNA.

In the interval between two scheduled visits, patients have access to medical personnel whenever they become ill.

## Drugs

In accordance with WHO and Vietnamese guidelines, the standard HCV treatment in DRIVE-C is sofosbuvir 400 mg/day and daclatasvir 60 mg/day for 12 weeks. The choice of DAA regimen was based on our willingness to have a pan-genotypic regimen and to use drugs already registered in Vietnam, to allow quick scale up of the model if effective, while taking into account the potential interactions with ART for co-infected patients.

For HIV-infected participants receiving efavirenz or nevirapine, daclatasvir dose is increased to 90 mg/day. In case of cirrhosis, ribavirin is added to sofosbuvir/daclatasvir during the 12 weeks of treatment. Cirrhosis is defined by a Fibroscan value >12.5 kPa.[20 21] In case of ribavirin contraindication or side effects leading to ribavirin discontinuation, sofosbuvir/daclatasvir combination is prescribed for 24 weeks. Sofosbuvir and daclatasvir are purchased from Hetero Drugs, a generic manufacturer granted by Gilead and BMS companies. Drugs are prescribed by study doctors and delivered by hospital pharmacists.

Patients receiving ART and/or MMT will start HCV treatment after at least 3 months of ART and 2 weeks of MMT. All participants are tested for hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (HBsAb) at preinclusion visit. Participants with positive HBsAg already treated initiate HCV treatment without delay. Participants with positive HBsAg not yet treated will be first treated for HBV. An appointment for HCV treatment initiation is provided within 1 month after HBV treatment initiation. Participants with negative HBsAg and HBsAb at preinclusion visit and who experience an elevation of ALT >5 times upper normal limit during HCV treatment FU will be retested for HBsAg and, if negative, tested for hepatitis B core antibody (HBcAb). In case of HBsAg or HBcAb positive, HBV DNA is measured to detect possible HBV flare-ups or reactivation as recommended by the WHO. Tenofovir will be introduced in case of detectable HBV DNA. HBV immunisation is recommended to participants with negative HBsAg and negative HBsAb.

## Role of peer educators

Seven CBO, coordinated by the Vietnamese non-governmental organisation Supporting Community Development Initiatives, are involved in DRIVE-C. CBO members both intervene (1) in the three hepatitis clinics, where they provide counselling and conduct questionnaires, and (2) in the field where each CBO member is assigned participants to follow and support on a regular basis to overcome potential obstacles regarding: access to MMT and/or ART, adherence to HCV treatment, administrative tasks and access to harm reduction materials. They are also in charge of counselling and tracing participants for missed study visits.

## Data collection and data management

The data collected are recorded in an electronic case report form (CRF), using the Ennov Clinical software accredited by the US Food and Drug Administration (FDA). They include: sociodemographic information, medical history, clinical evaluation, laboratory test and imaging results, drug uptake, adverse events, social events,

**Table 1** Schedule of study visits and assessments (for patients treated for 12 weeks).

| Study procedures | Screening | Visit 1<br>Pre-inclusion | Visit 2<br>Inclusion/ treatment initiation | Visit 3<br>Week 2 Treatment FU | Visit 4<br>Week 4 Treatment FU | Visit 5<br>Week 8 Treatment FU | Visit 6<br>Week 12 End of treatment | Visit 7<br>Week 24 Treatment evaluation (SVR12) | Visit 8<br>Week 36 FU | Visit 9<br>Week 48 End of the study |
|---|---|---|---|---|---|---|---|---|---|---|
| Verification of eligibility criteria | | × | | | | | | | | |
| Information about the study | × | × | | | | | | | | |
| Signature of consent form | × | × | | | | | | | | |
| HCV-related counselling session | | × | × | | | | × | × | × | × |
| Treatment adherence support | | | × | × | × | × | | | | |
| Drug delivery | | | × | × | × | × | | | | |
| Pill count | | | | × | × | × | × | | | |
| Questionnaires | | | | | | | | | | |
| Alcohol use—AUDIT | | × | ×* | | | | | × | | × |
| Quality of life—EQ-5D-5L | | × | ×* | | | × | | × | | × |
| Sexual, drug use and other behaviours | | × | ×* | | | × | | × | | × |
| Physical examination, including assessment of adverse events | | × | × | × | × | × | × | × | × | × |

Continued

**Table 1** Continued

| Study procedures | Screening | Visit 1 Pre-inclusion | Visit 2 Inclusion/ treatment initiation | Visit 3 Week 2 Treatment FU | Visit 4 Week 4 Treatment FU | Visit 5 Week 8 Treatment FU | Visit 6 Week 12 End of treatment | Visit 7 Week 24 Treatment evaluation (SVR12) | Visit 8 Week 36 FU | Visit 9 Week 48 End of the study |
|---|---|---|---|---|---|---|---|---|---|---|
| Complete blood count | | × | ×† | ×‡ | × | ×‡ | | | | × |
| Serum creatinine | | × | ×† | ×‡ | × | ×‡ | | | | × |
| AST/ALT | | × | ×† | ×‡ | × | ×‡,§ | ×§ | | | × |
| GGT, ALP and bilirubin | | × | | | | | | | | ×§§ |
| Albumin and prothrombin time | | | ×‡‡ | | | | | | | ×‡‡ |
| HBsAg and HBsAb | | × | | | | | | | | |
| Pregnancy test | | ×¶ | ×¶† | | ×¶ | ×¶ | ×¶ | ×¶ | ×** | |
| HCV RNA | × | | | | | | | × | | × |
| HCV genotyping | | ×*** | | | | | | ×†† | | ×†† |
| Abdominal ultrasound | | × | | | | | | ×‡‡ | | ×‡‡ |
| Fasting FibroScan | | ×¶¶ | | | | | | | | ×‡‡ |
| Storage of frozen plasma | | × | ×† | | × | | × | × | | × |
| Storage of frozen dried blood spot | | × | ×† | | × | | × | × | | × |

Continued

Table 1 Continued

| Study procedures | Screening | Visit 1 Pre-inclusion | Visit 2 Inclusion/ treatment initiation | Visit 3 Week 2 Treatment FU | Visit 4 Week 4 Treatment FU | Visit 5 Week 8 Treatment FU | Visit 6 Week 12 End of treatment | Visit 7 Week 24 Treatment evaluation (SVR12) | Visit 8 Week 36 FU | Visit 9 Week 48 End of the study |
|---|---|---|---|---|---|---|---|---|---|---|

*If more than 3 months between preinclusion and inclusion, or if patient started ART or MMT since preinclusion visit.
†If introduction of HCV treatment occurs >4 weeks after preinclusion visit.
‡If treatment regimen contains ribavirin.
§For patients with HBsAg positive and patients with HBsAg negative and HBsAb negative.
¶For women of childbearing age.
**For women of childbearing age with treatment regimen containing ribavirin.
††For patients with HCV VL ≥10 IU/mL.
‡‡For patients with cirrhosis.
§§For patients with cirrhosis but only bilirubin.
¶¶For patients followed in Viet Tiep Hospital and for patients followed in Kien An Hospital and in Thuy Nguyen Hospital with APRI score >1.
***Baseline HCV genotyping will be batch performed.
ALP, alkaline phosphatase; ALT, alanine transaminase; APRI, AST to Platelet Ratio Index; AST, aspartate transaminase; AUDIT, Alcohol Use Disorder Identification Test; FU, follow-up; GGT, gamma-glutamyltransferase; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; SVR12, sustained virological response at post-treatment week 12; VL, viral load.

including incarceration, alcohol use: Alcohol Use Disorder Identification Test, quality of life: EQ-5D (Euro-Qol-5D),[22] sexual, drug use and other behaviours self-reported by participants and focusing on HCV infection or reinfection risks.

Verification of the completeness and consistency of the data is performed according to a specific data validation plan. Data management is performed both at the international coordinating trial unit (CTU) level (Pathogenesis and Control of Chronic Infections, UMR 1058–INSERM, Univ Montpellier, EFS, Montpellier, France) and at the local CTU level when feasible (Faculty of Public Health, Haiphong University of Medicine and Pharmacy, Hai Phong, Vietnam). Centralised queries are sent by the international CTU to the local CTU and by the local CTU to study clinical sites under the terms of the verification defined in the data validation plan.

## Safety reporting

All biological and clinical adverse events (AE) are reported in a specific CRF AE form, and all serious adverse events are notified to the sponsor, who is responsible for the assessment of their causality in relation to the study drugs, concomitant medication and the research.

## Sample size

### Power calculation for the model of care assessment

DRIVE RDS3 survey aims to enrol 1500 participants. According to DRIVE first and second rounds of RDS data, we expect the number of participants at each step as described in figure 2. These numbers will provide us with a precise estimation of outcomes. The proportion of PWID with HCV chronic infection who are cured is expected to be 90%×90%×90%=73%. The enrolment of about 900 PWID with HCV chronic infection will allow estimating the expected cure rate of 73% with a precision of ±2.9%. With a lower cure rate of 50%, we would have a similar precision of ±3.3%.

According to DRIVE RDS2 and FU data, an estimated 567 cohort participants, not having attended the RDS3 will be screened for hepatitis at cohort FU visits.

A total of 1050 patients will be included in the study. This number of patients will allow us to explore the treatment-response heterogeneity, partly through subgroup analyses based on key characteristics, such as HIV co-infection, liver fibrosis stage or genotypes. Finally, enrolling all HCV-infected individuals identified in one mass screening round (RDS) as a unit will allow the mathematical model to estimate to what extent the repetition of RDS could tackle HCV transmission in Hai Phong.

### Power calculation for the reinfection rate

Among the 650+295=945 patients cured (SVR12), we estimate that 90% (850) will be assessed for reinfection at week 48. Based on these assumptions and setting the alpha risk to 5%, we will be able to estimate an expected reinfection rate of 3% with a precision of ±1.3%, or an expected reinfection rate of 5% with a precision of ±1.6%.

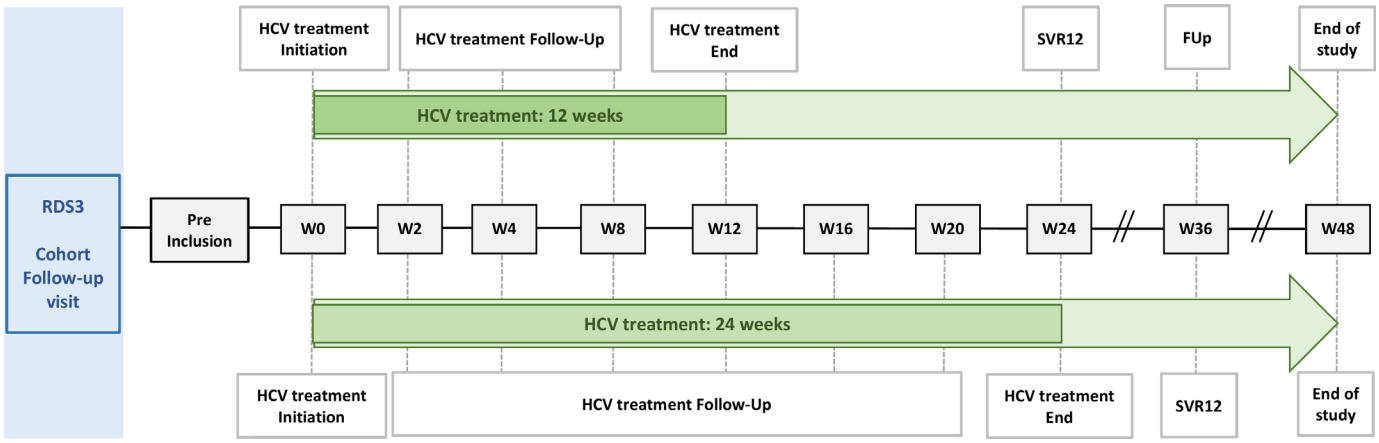


**Figure 1** Patient visit schedule flowchart. HCV, hepatitis C virus; FUp, follow-up; RDS, respondent-driven sampling; W0, week 0; SVR12, sustained virological response at post-treatment week 12.

## Analysis strategies

For the intention to treat analysis, the model of HCV care will be analysed separately for the DRIVE RDS3 and for cohort FU visits participants. The latter will reflect the ability to treat and cure all the HCV-infected patients who are already in HIV and addiction care. For each analysis, all participants will be included in the analysis, whatever their FU (including patients who died, were lost to FU, or withdrew from the study). For the on-treatment analysis, we will consider only patients who started HCV treatment.

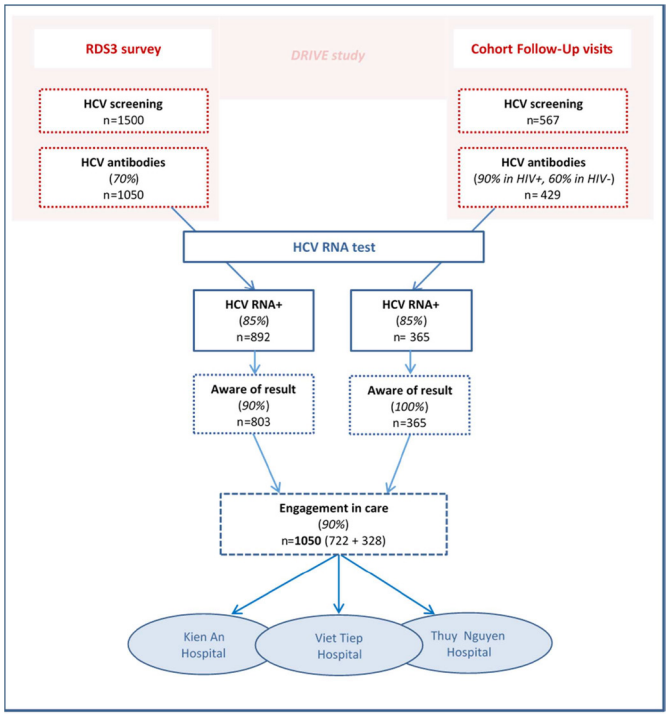


**Figure 2** Study pre-enrolment diagram. HCV, hepatitis C virus; RDS3, third respondent-driven sampling.

## Statistical methods

A detailed plan of analysis will be elaborated and validated by the Scientific Advisory Board (SAB) before the end of enrolment.

The proportion of patients who have met the primary outcome (ie, plasma HCV RNA below 10 IU/mL at week 48) will be calculated with its 95% CI. The primary outcome will be compared with a theoretical value of 70% (rounded from 73%) using a classic one-sided test based on an approximation by the normal distribution. This value represents the expected rate of patients with chronic HCV infection who will be cured. The primary outcome will then be calculated in subgroups, such as gender or type of drug use.

All secondary outcomes will be described with their 95% CI. We will then investigate the treatment-response heterogeneity, whereby some PWID may adhere or respond differently to the treatment because of measurable characteristics. For this purpose, we will use a logistic regression model to identify the factors associated with failure to cure, as well as subgroup analyses (including gender and HIV infection) to assess the cure rate variations across the population characteristics.

The approaches to deal with missing data will be described in the detailed plan of analysis. In brief, the primary and secondary outcomes will be evaluated according to a complete case analysis. In order to assess the factors associated with outcomes failures, we will use a multiple imputation approach to replace missing data when they represent more than 1% of all data for a given variable.

## Modelling and cost-effectiveness analysis

Mathematical modelling, developed by a team from Department of Population Health Sciences at the University of Bristol, the United Kingdom, will be used to estimate the impact and cost effectiveness of scaling up the HCV care model, compared with the baseline level of prevention and treatment. The model will be adapted from an existing open dynamic, deterministic model

of HCV transmission, progression and HCV treatment among PWID and ex-PWID communities.[18 23 24] The model will be fit within a Bayesian framework to epidemiological, behavioural and intervention related data from the DRIVE and DRIVE-C study. Crucially, the model will be able to account for the 'prevention benefit' of treatment as well as reduction in HCV-related morbidity. The impact modelling will consider if the intervention could reduce HCV transmission to low levels (90% reduction in HCV incidence and mortality) among PWID in the next 5–15 years, as set out by the recent WHO elimination targets.[3] Expenditure data will be collected from the DRIVE-C intervention with direct and indirect costs allocated to activities, such as diagnosis, baseline assessment, treatment initiation and FU visits. Staff costs will be assigned to activities based on average length of visits using time sheets completed by patient-facing personnel. Unit costs for laboratory tests and medicines will be taken from invoices or price lists where relevant. The cost per patient will be calculated using resource use data from the study for each patient tested or treated for HCV. Quality of life data (EQ-5D-5L)[22] will be collected as part of the study to estimate changes in utility due to treatment. The cost-effectiveness analysis will estimate the mean ICER in terms of cost per QALY saved, which will be compared against standard thresholds for interventions being cost effective in LMIC.[25 26]

## Patient and public involvement

CBO members, as peer educators and, for those infected with HCV, as patients' representatives, have been involved since the very beginning in the process of study design and implementation through brainstorming sessions, including identifying the research questions. They provided an insight into patients' needs and the currently existing gaps in the health system regarding the specific population of PWID. They took part in elaborating the procedures, the information notice, the consent form and other tools dedicated to patients, such as counselling materials. Through the RDS survey strategy, patients participate in recruiting other patients in the study.

## Study oversight

The overall management of the study is carried out by the coordination team composed of the two co-principal investigators, and the international and local CTU.

An SAB is established to ensure the proper conduct of the trial across its scientific, methodological, and ethical aspects and the protection of participants. This SAB includes members of the coordination team, external experts and representatives of PWID.

An independent Data and Safety Monitoring Board (DSMB) will review data in order to advise the sponsor and the SAB. The DSMB monitors the main safety and efficacy outcome measures and the overall conduct of the study, with the aim of protecting the safety and the interests of the study participants. It is composed by experts in hepatitis C clinical management and statistics.

## DISCUSSION

Although DAA drugs allow achieving very high rates of HCV cure among patients (at the individual level), we still do not know how to integrate DAA in the health system in LMIC, and whether HCV elimination can be achieved at the population level among high-risk groups, such as PWID. Our research could demonstrate that an integrated model of care, including a simplified treatment protocol accounting for comorbidities (addiction and HIV), and important support from CBO for linkage to care after screening, DAA adherence and prevention of reinfection after cure could lead to achieve high rate of HCV cure among PWID screened with chronic hepatitis C. The modelling and cost-effectiveness analyses will show to what extent this model of care, if scaled up through repeated RDS, could lead rapidly to HCV elimination and is worth the initial investment. The reinfection rate issue will not be fully addressed in this project because of the limited FU after SVR12. However, recent information suggest that this rate is the highest shortly after cure and then decreases with time. The DRIVE-C results, first research on assessing the efficacy of a model of HCV care among PWID in Vietnam, will inform decision-makers and will support replication and adaptation of the intervention to other contexts.

## Ethics and dissemination

### Study approval

The protocol was approved by Haiphong University of Medicine and Pharmacy's Ethics Review Board and the Vietnamese Ministry of Health.

### Consenting participant

Potential participants are informed by the investigator verbally and via the information sheet of the objectives, duration, potential risks and benefits of the study, of any discomfort it may entail, and that they are free, without justification, to withdraw at any time. The investigator ensures the participant understanding and adequate answers to all his/her questions before the signature of the consent form (online supplemental file 1). The study is free of charge for participants who receive financial compensation only for the transportation costs.

### Confidentiality

All data recorded in the framework of this study, including subject medical information, are strictly confidential and coded, using a unique study subject identification code. Access to participant data is restricted to investigators and appropriate study staff. Published results will not contain any personal identifying data. In case of consent withdrawal, no new information will further be collected and recorded in the database. The data collected prior to the withdrawal will be used for the analysis, unless the participant expresses the will that his/her data be removed from the database.

### Care of peer educators

All CBO members involved in the DRIVE-C study and their partners are proposed to be tested for HCV. When

diagnosed with a chronic hepatitis C, they receive therapeutic education and free HCV treatment.

## Dissemination plan

Final results are expected by mid-2021. Relevant results will be shared with participants, investigators and national authorities, disseminated through peer-review international journals and presented at national and international conferences, as well as community-based events organised in Vietnam.

## Trial status

PWID eligible for DRIVE-C were identified from October 2018 to May 2019, and enrolment in the study started in November 2018. Among 1201 eligible participants, 1022 were referred to hepatitis clinics. HCV treatment initiation and FU are ongoing.

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***THIS DRAFT OF THE INFORMATION NOTICE HAS BEEN DISCUSSED AND PREPARED TOGETHER WITH COMMUNITY-BASED ORGANIZATIONS' MEMBERS IN HAI PHONG CITY***

# Information sheet

## DRIVE-C (DRug use & Infections in ViEtnam – Hepatitis C)

Towards HCV elimination: Evaluation of an integrated model of care targeting people who inject drugs in Hai Phong, Vietnam.

**ANRS N° 12380 DRIVE-C**

Version n°2.0 of 22/10/2018 approved by HPMU IRB on 26/10/2018

COORDINATING INVESTIGATOR: ***Dr PHAM MINH KHUE***

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Study is sponsored and funded by Inserm-ANRS (National Institute of Health and Medical Research, France Research North & South HIV/AIDS and Hepatitis), 101 rue de Tolbiac, Paris 75013

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**- This information sheet is performed to help you in making decision regarding your participation in the study described below.**

**- You are free to answer "yes" or "no" to the question that you are asked: "Do you want to participate in this study?"**

**- You have the right to take time to think, to discuss on this study and to ask any questions you want to whom you want.**

**- If you do not want to participate in this study, you will continue to benefit from the best care possible.**

**- You can change your decision and ask to stop participating in this study at any time you want. You will continue to receive the best care that your doctor can offer. We simply ask you to inform us about your decision as soon as possible.**

Dear Madam/Sir,

You have recently taken part in the DRIVE study: "DRug use and Infections in ViEtnam: ending the HIV epidemic among people who inject drugs in Hai Phong, Vietnam". According to the blood test performed within this study, you have a disease called hepatitis C. Hepatitis C is very frequent among people who inject drugs (PWID) in the world, notably in Vietnam with more than 60% of PWID infected.

Hepatitis C is caused by the hepatitis C virus (HCV), which is passed from an infected person to another through the same routes of transmission as HIV. When a person is infected with HCV, the virus goes to the liver, where it multiplies and causes inflammation and the death of liver cells. Sometimes the body gets rid of the virus, or accepts the virus and there is no liver damage. In other cases when the body cannot eliminate the virus by itself, the person becomes chronically infected. Overtime in chronic infection, the dead liver cells are replaced by excessive scar tissue that invades the liver, something that doctors call "fibrosis". At the late stage of fibrosis, named "cirrhosis", the liver is much damaged. At some point the liver can even stop working. This is called liver failure and it can lead to death. Some people with cirrhosis can also develop liver cancer.

There is a new, short-term, treatment against hepatitis C that is very efficient and presents few side effects. This treatment is becoming available in Vietnam but still difficult to obtain because not yet covered by the health insurance.

In order to develop a therapeutic strategy for a better management of HCV infection in resource-limited settings like Vietnam, an efficient model is needed. In our experience, the model used for the DRIVE study that you participated in could be adapted for HCV infection. In a wider perspective, this model may have the potential to eliminate HCV among PWIDs.

Because you participate in the DRIVE study and you have hepatitis C, we want to propose to you to participate in this specific study, called DRIVE-C, which will give you access to HCV treatment as described in detail below.

This study is conducted by Vietnamese researchers from the Hai Phong University of Medicine and Pharmacy and from Viet Tiep Hospital, in collaboration with researchers from France and England. The study has been approved by the Ministry of Health, the Institutional Review Board of Hai Phong University of Medicine and Pharmacy and authorized by Hai Phong authorities as well as relevant institutions in France.

It will be conducted according to the national and international rules for research. Before deciding whether you agree to participate in the study, a study doctor will give you all the detailed information about the study written in this document. Please take time to read this information carefully and ask anything that you do not understand.

## OBJECTIVES OF THE STUDY

**The primary objective of this study is to assess the effectiveness of a model of hepatitis C infection screening and care targeting PWIDs in Hai Phong, Vietnam**.

This model will encompass all steps involved in achieving HCV cure among individuals identified with hepatitis C:

i) Mass detection of PWIDs with hepatitis C;
ii) community-based support to improve referral to specific care;
iii) HCV simplified treatment delivered in hospital-based clinics;
iv) optimized treatment adherence;
v) harm reduction activities to encompass HCV transmission risk and prevention of HCV reinfection



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## PARTICIPATION IN THE STUDY

You have full freedom in accepting or refusing to participate in this project.

**If you refuse to participate in this study**, you will be proposed a referral to another hepatitis C specialist.

**If you accept to participate in this study**, you are invited to sign the consent form attached to this document that will also be signed by the medical doctor who offered you to participate in this study. You will also be offered to keep a copy of this form. **After signing the consent form**, you will undergo the pre-inclusion visit.

Women cannot participate in the study if they are pregnant. If it turns out that some conditions do not allow you to participate in the study, the medical doctor will explain the reasons and decide with you the most appropriate medical care.

## DETAILED FOLLOW-UP & TREATMENT

Around 1.050 patients will be enrolled in the study. The overall duration of the study will be 3 years.

Each patient will be followed up to 12 months after treatment initiation.

During the 12 months of this study, you will attend at least 9 visits with trained doctors in one of the 3 HCV clinics selected for the study, and get your blood checked at least 5 times for a total quantity of 68 ml in the entire study. This amount of blood sampling is not dangerous for your health at all.

During the whole study period, you can come to the hospital whenever you have any health problems, your doctor will suggest you undergo additional tests if needed.

For your safety, a Scientific Committee and an independent Data Safety and Monitoring Board will regularly meet to examine all new information related to the study (new data on treatment, new patient facts…) and monitor its correct implementation. They might decide to prematurely stop the study for safety reason.

**Visit 1 (Pre-inclusion visit):** During this visit, doctor and counselor will explain carefully all aspects of DRIVE-C study, and will answer your questions. Once enrolled in the study, an assessment of your health will be performed through a physical examination, blood tests, liver stiffness assessment, abdominal ultrasound and pregnancy test for women of childbearing age. Your blood will also be collected for the purpose of storage. You will be interviewed on your sexual and drug use behaviors (with focus on HCV infection risks) and on your quality of life. If you want, you will follow an HCV-related counseling session.

- If you present a severe associated disease requiring specific treatment or any clinical conditions, which might compromise the safety of HCV treatment, then you will not be proposed to initiate the HCV treatment.
- For woman: if you are pregnant or if you refuse to use a contraceptive method, then you will not be proposed to initiate the HCV treatment.

If you respond to all inclusion criteria, then you will be appointed within one to two week(s) for a second visit in the hepatitis clinic for initiating HCV treatment.

- If you are **co-infected with HIV** and **do not receive ART**, you will be offered to be referred to an OPC (outpatient clinic) for HIV care.
- If you are **co-infected with HBV** and require **treatment**, you will be offered to be referred to an specialist for HBV care.
- If you **do not receive MMT** (Methadone Maintenance Treatment), you will be offered to be referred to a methadone clinic for methadone initiation.
- In those cases, your second visit for initiating HCV treatment will be planned within 1 to 3 month(s) after starting ART, HBV treatment and/or methadone. The research staff will provide assistance and address all potential obstacles for you to enroll in care, including administrative issues.



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**Visit 2** (HCV treatment initiation): after clinical examination and before initiating the treatment, you will follow a session of therapeutic education including adherence counseling. You will receive a treatment for your hepatitis C based on the combination of two medicines already used in many countries, sofosbuvir and daclatasvir, that is highly efficient and recommended by the Vietnamese Ministry of Health for a total duration of 12 weeks.

The basic posology will be {one tablet of sofosbuvir 400-mg + one tablet of daclatasvir 60-mg} per day. For participants receiving efavirenz or nevirapine, daclatasvir dose will be adjusted to 90 mg/day.
In case of cirrhosis, ribavirin will be added to sofosbuvir/daclatasvir at a dose adapted to the patient weight (for patients < 75kg: 2 x 500 mg tablets per day). In case of ribavirin contra-indication, sofosbuvir-daclatasvir will be used for 24 weeks.

In order to ensure your safety during this study, you will be invited to return to the hepatitis clinic at 2, 4, 8, 12, 24, 36 and 48 weeks after the initiation of your treatment. You can return more frequently if you present any side effects of the treatment, if you have any questions about your health status or if you have any abnormal signs/symptoms.

By participating in the study, you agree to take the drugs according to the instructions provided by your study doctor and to come to the clinic for the scheduled study visits. For your own safety, you have to inform your study doctor about your health status and about all medicines, including prescription, over-the-counter (non-prescription), and herbal or alternative medicines you are taking. This is because there may be serious side-effects when other medicines are taken together with HCV treatment.

At week 2 (**Visit 3**), week 4 (**Visit** 4) and week 8 (**Visit 5**), you will benefit from a clinical check-up and treatment adherence support session. At Visit 4, biological check-up will be done again to confirm the tolerance of the HCV treatment and your blood will also be collected for the purpose of storage. No systematic blood test will be performed at Visit 3 and Visit 5, but doctor can ask if necessary. At visit 5, you will be interviewed on your sexual and drug use behaviors and on your quality of life.

At week 12 (**Visit 6**), corresponding to the end of treatment, you will undergo clinical examination, and HCV-related counseling session focusing on HCV re-infection risks. Your blood will be collected for the purpose of storage.

At week 24 (**Visit 7**), you will undergo clinical examination, interview on your sexual, drug use behaviors and your quality of life, and blood collection notably to assess the efficacy of HCV treatment by dosage of HCV virus circulating in blood. Your blood will also be collected for the purpose of storage, and you will undergo an HCV-related counseling session focusing on HCV re-infection risks.

At week 36 (**Visit 8**), you will undergo clinical examination and you will be informed if you are cured from HCV or not.

- If you are cured, you will undergo HCV-related counseling session where prevention of reinfection will be emphasized.
- If you are not cured, your doctor will assess the reasons of treatment failure. According to expert committee recommendations and drugs available in Vietnam, a new therapeutic plan could be proposed.

At week 48 (**Visit 9**), if you were cured at week 36, you will undergo clinical examination, interview and blood collection. You will be assessed for HCV re-infection. Your blood will also be collected for the purpose of storage, and you will undergo an HCV-related counseling session focusing on HCV re-infection risks.

For the success of the study, it is very important that you follow the visit schedule. If you cannot attend a visit, please inform your study doctor so that he/she can find another appointment with you. If you cannot attend a study visit and do not contact your study doctor, the study team will contact you by telephone or through the Community Based Organization worker who support you to know the reasons.

During the whole duration of the study, researchers may collect medical routine data about you in Hai Phong methadone programs and infectious disease clinics if you are participating in methadone treatment, HBV care or HIV care. They may also access and use your data collected within DRIVE study.

## POSSIBLE BENEFITS AND RISK/DISAVANTAGES OF TAKING PART

**What are the benefits of participating in this study?**

You will contribute to the answer of what is the best strategy to cure hepatitis C. It is a very important answer for all the PWIDs with chronic hepatitis C in Vietnam and in the whole world.

You will benefit from a new HCV treatment whatever the stage of your disease. The duration of the treatment is short. You will also benefit from thorough examinations to monitor your treatment, especially the HCV viral load in the blood, as well as access to HCV genotyping.

You will benefit from HCV-related counselling with respect to how you can protect your health and prevent being re-infected and from peer-support along the whole period of the study. The CBOs' members will assist you to address all potential obstacles to enrol in care, including administrative issues.

You will not pay any costs related to this study. The costs of the biological and radiological diagnosis, and hospitalization, if necessary, will be covered by the study.

Your participation is entirely voluntary and you will not receive any financial compensation except transportation expenses for all protocol visits.

**What are the possible risks of being in the study?**

HCV drugs can produce side-effects. The most common adverse events of these medications are: headache, fatigue, insomnia. Others can be: dizziness, migraine, nausea, diarrhea, abdominal pain, arthralgia or myalgia. Ribavirin added to sofosbuvir/daclatasvir for cirrhotic patients, can sometimes give anemia, decreased appetite, irritability, hot flush, dyspnea, dyspnea exertional, cough, nasal congestion, vomiting, gastroesophageal reflux disease, constipation, dry mouth, flatulence, rash, alopecia, pruritus or dry skin. Therefore, we will check for abnormalities in your blood during your follow-up visits. It is very important for you to be aware of it, and you will have to come back to see your doctor whenever you are sick so that the doctor can identify the cause of your illness and cure it.

Some people feel uncomfortable about being asked personal questions. Remember that you can refuse to answer any question that you do not want to. All information you provide for this study will be confidential.

Some people experience discomfort when blood is drawn and may feel dizzy or even faint. You may have a bruise or swelling where the needle goes into your arm. Some people may develop an infection where the needle goes into the arm, but this is very rare. In order to decrease this risk, our study nurses are well trained and qualified for the procedure.

The greatest risk may involve your privacy and confidentiality. We have considered this very carefully. Loss of confidentiality could cause other people to discriminate against you and could cause problems in your family and personal relationships. The steps to protect your privacy are described below.

## HOW WILL MY PRIVACY BE PROTECTED?

**What will happen to the information you give us?**

To protect your privacy, you will participate under a study code only, and your name will never appear in any study materials, blood samples, database or reports. Only codes will be used. The only study document with the name you provide to us and your code will be kept in a locked file at the hospital. Only study staff conducting the study and sponsor representatives can have access to your data and they are responsible for

your confidentiality. Any report or publication that results from this study will not use your name or identify you personally.

## HOW THE DATA IS PROCESSED?

As part of the study you may participate in, a treatment of your personal health data is implemented to analyze the results of the study with regard to the objectives.

The sponsor of the study, Inserm-ANRS, is a French research agency that fulfills a public interest mission. This justifies the processing of health data and data relative to (geographical origin, data relating to your sex life, etc.) for scientific research purposes, under European and French regulations.

In the event that your personal data are not collected directly from you, the source from which the data comes is your medical file.

The data processing will always be executed with guarantees of protection ensuring their confidentiality (use of a code).

**Data transfer**

Your data may be transferred to national or French or health authorities (drug agency ...), to other national or international private or public research teams. The data thus transmitted will be framed by appropriate and adapted guarantees provided in a contract / sharing agreement between Inserm-ANRS and the recipient (s) of the data under conditions guaranteeing the confidentiality of your data. Information on the purpose of the treatment through a newsletter will be sent to you at the appropriate time.

**Your rights:**

In accordance with the French law n ° 78-17 of 6 January 1978 amended in particular by Law 2018-493 of June 20, 2018, relating to Technology Data Files and Civil Liberties, you have a right to rectify your data collected, the right to oppose (right to opposition) or to limit their use (right to limitation of treatment).

Please note that in accordance with Article 17 of the General Data Protection Regulations (GDPR) to ensure compliance with Article L.1122-1-1 of the French Public Health Code, insofar as the erasure of data may make it impossible or seriously jeopardize the achievement of treatment goals, data collected prior to the withdrawal of your consent may not be erased and may continue to be processed under conditions that will ensure their minimization and confidentiality

You can also access, directly or through a doctor of your choice, all of your medical data in application of the provisions of Article L 1111-7 of the French Public Health Code.

The responsible of the data processing is the research sponsor (Inserm-ANRS) whose contact details are given on page 1 of this document.

If you have any questions regarding these rights or to obtain a copy of the contractual documents related to the transfer of your data, you can contact the doctor who will follow you in the course of the research.

In addition, the Data Protection Officer of Inserm is available for any question related to the processing of your data or the exercise of your rights by mail (dpo@inserm.fr) or by post (Delegate to data protection, INSERM, 101 rue de Tolbiac, 75013 Paris)

Finally, you have the right to lodge a complaint with the French supervisory authority: the CNIL (National Commission for Information Technology and Liberties).

Your data will be kept in accordance with current archiving regulations for clinical research.

## CAN I WITHDRAW FROM THE STUDY?

You can withdraw from this study whenever you wish. A last visit will then be done and your medical doctor will propose you a list of hepatitis C specialists to be referred to. Moreover, your participation in the study can be stopped by your doctor if s/he thinks it is necessary (to protect your safety or if you do not follow the research procedures). National Health Authorities or the Scientific Committee who monitors this study may also decide to end it.

Your doctor may stop prescribing you or changing you to another drug before the study ends if the continued use of research drugs can be harmful to you or if you cannot take study medication as prescribed in the protocol. If you must stop taking medication before the end of study, your doctor will recommend that you continue to participate in the study and return to the hospital for completion of all follow-up visits.

If you withdraw from the trial, you can express the will that your data be removed from the database and your laboratory samples be destroyed. If you do not express such will, data and samples collected prior to the date of your consent withdrawal could be used by the team.

## WHAT HAPPENS AT THE END OF THE TRIAL?

At the end of the study, the results will be disseminated to participants & PWID community through presentations and open discussions organized by the study's CBOs in their offices. At the end of the trial, you will be able to debrief with your study doctor about your participation and experience during the study. If you have cirrhosis, then your doctor will advise you about necessary regular follow-up with abdominal ultrasound for surveillance of liver cancer.

If you are cured, you will need to prevent from HCV reinfection, according to all information that were provided to you during the study counseling sessions.

## WHAT HAPPENS IF THERE IS A PROBLEM?

In case of problem, you should report it to your doctor.

For woman: if you become pregnant during the HCV treatment period, then you should inform your doctor. S/he will decide if the treatment must be discontinued for your fetus safety.

As sponsor, the Inserm-ANRS has taken an insurance policy which guarantees compensation if you experience any harm as a direct result of your involvement in this study.

## BIOLOGICAL SAMPLE STORAGE:

Some blood samples will be frozen for future HCV or drug use related research. Some analysis may not be available in Vietnam, therefore, blood samples may be sent overseas to accomplish additional researches. Providing your written consent, these samples will be kept anonymously in freezers in the laboratory of Hai Phong University of Medicine and Pharmacy. They will only be used for approved studies by Ethic Committees and regulatory authorities, in Vietnam or abroad. If genetic studies are planned with the stored blood, you will be asked again for your consent.

The expected duration of conservation is a maximum of 25 years.

The transfer of biological samples and data will be framed by appropriate safeguards and adapted provided in a contract / sharing agreement between the representative of Inserm-ANRS and the recipient (s) of the samples or data under conditions guaranteeing the confidentiality of your data.



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## CONTACT FOR FURTHER INFORMATION

During the study period, you can ask any question or request for additional information from your doctor or the person in charge of this study: Doctor PHAM Minh Khue (Hai Phong University of Medicine and Pharmacy). Phone number: 013 66 22 422

**ANRS N° 12380 DRIVE-C**

**Version n°1.0 of 27/04/2018 approved by HPMU IRB on 31/05/2018**

# CONSENT FORM *Version 1.0*

**Declaration by Participant**

By signing below, I ……..……. agree to take part in the ***DRIVE-C study*** *(DRug use & Infections in ViEtnam – Hepatitis C): Towards HCV elimination: Evaluation of an integrated model of care targeting people who inject drugs in Hai Phong, Vietnam.*

- I have read or have been read the information notice attached with this form; I have understood the objective, advantages and disadvantages of the study, and the form is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurized to take part.
- I may choose to leave the study at any time and will not be penalized or prejudiced in any way.
- I accept that study team and any person involved in the study have access to my information according to the confidentiality rules.
- I accept that all confidential data collected for this study will be encoded and recorded in a computerized database.
- By signing this consent form, I have not waived any of the legal rights that I have as a participant in a research study.
- At the end of the study, I could be informed of the overall results of this research.
- I will be given a signed copy of this consent form and information sheet.

**I agree** to have my left over blood stored and tested for future research related to HCV, or other drug related diseases, in Vietnam or overseas:

Yes ☐ No ☐

**I agree** that the researchers may check with Hai Phong methadone programs and infectious disease clinics to see if I am participating in methadone treatment or HIV care and to collect medical routine data in the next 12 months. I also agree that they access and use my data collected within DRIVE study.

Yes ☐ No ☐

Signed at (*place*) ..... on (*date*) ..... 201_.

..... .....

Signature (or Thumbprint) of Participant Signature of Witness (if applicable)

**Declaration by the Investigator**

I *(name)* ..... declare that:

- I explained the information in this document to .....
- I encouraged the participant to ask questions and took adequate time to answer them.
- I am satisfied that the participant adequately understands all aspects of the research, as discussed above
- An interpreter was present during the information process: Yes ☐ No ☐

(*If an interpreter is used then the interpreter must sign the declaration below.)*

Signed at (*place*) ..... on (*date*) ..... 201_.

..... .....

Signature of Investigator Signature of interpreter (if applicable)



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***THIS DRAFT OF THE INFORMATION NOTICE HAS BEEN DISCUSSED AND PREPARED TOGETHER WITH COMMUNITY-BASED ORGANIZATIONS' MEMBERS IN HAI PHONG CITY***

# Information sheet

## DRIVE-C (DRug use & Infections in ViEtnam – Hepatitis C)

Towards HCV elimination: Evaluation of an integrated model of care targeting people who inject drugs in Hai Phong, Vietnam.

**ANRS N° 12380 DRIVE-C**

Version n°2.0 of 22/10/2018 approved by HPMU IRB on 26/10/2018

COORDINATING INVESTIGATOR: ***Dr PHAM MINH KHUE***

ADDRESS: ***Faculty of Public Health,***
***Hai Phong University of Medicine and Pharmacy***
***72A, Nguyen Binh Khiem, Ngo Quyen,***
***Hai Phong***

Study is sponsored and funded by Inserm-ANRS (National Institute of Health and Medical Research, France Research North & South HIV/AIDS and Hepatitis), 101 rue de Tolbiac, Paris 75013

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**- This information sheet is performed to help you in making decision regarding your participation in the study described below.**

**- You are free to answer "yes" or "no" to the question that you are asked: "Do you want to participate in this study?"**

**- You have the right to take time to think, to discuss on this study and to ask any questions you want to whom you want.**

**- If you do not want to participate in this study, you will continue to benefit from the best care possible.**

**- You can change your decision and ask to stop participating in this study at any time you want. You will continue to receive the best care that your doctor can offer. We simply ask you to inform us about your decision as soon as possible.**

Dear Madam/Sir,

You have recently taken part in the DRIVE study: "DRug use and Infections in ViEtnam: ending the HIV epidemic among people who inject drugs in Hai Phong, Vietnam". According to the blood test performed within this study, you have a disease called hepatitis C. Hepatitis C is very frequent among people who inject drugs (PWID) in the world, notably in Vietnam with more than 60% of PWID infected.

Hepatitis C is caused by the hepatitis C virus (HCV), which is passed from an infected person to another through the same routes of transmission as HIV. When a person is infected with HCV, the virus goes to the liver, where it multiplies and causes inflammation and the death of liver cells. Sometimes the body gets rid of the virus, or accepts the virus and there is no liver damage. In other cases when the body cannot eliminate the virus by itself, the person becomes chronically infected. Overtime in chronic infection, the dead liver cells are replaced by excessive scar tissue that invades the liver, something that doctors call "fibrosis". At the late stage of fibrosis, named "cirrhosis", the liver is much damaged. At some point the liver can even stop working. This is called liver failure and it can lead to death. Some people with cirrhosis can also develop liver cancer.

There is a new, short-term, treatment against hepatitis C that is very efficient and presents few side effects. This treatment is becoming available in Vietnam but still difficult to obtain because not yet covered by the health insurance.

In order to develop a therapeutic strategy for a better management of HCV infection in resource-limited settings like Vietnam, an efficient model is needed. In our experience, the model used for the DRIVE study that you participated in could be adapted for HCV infection. In a wider perspective, this model may have the potential to eliminate HCV among PWIDs.

Because you participate in the DRIVE study and you have hepatitis C, we want to propose to you to participate in this specific study, called DRIVE-C, which will give you access to HCV treatment as described in detail below.

This study is conducted by Vietnamese researchers from the Hai Phong University of Medicine and Pharmacy and from Viet Tiep Hospital, in collaboration with researchers from France and England. The study has been approved by the Ministry of Health, the Institutional Review Board of Hai Phong University of Medicine and Pharmacy and authorized by Hai Phong authorities as well as relevant institutions in France.

It will be conducted according to the national and international rules for research. Before deciding whether you agree to participate in the study, a study doctor will give you all the detailed information about the study written in this document. Please take time to read this information carefully and ask anything that you do not understand.

## OBJECTIVES OF THE STUDY

**The primary objective of this study is to assess the effectiveness of a model of hepatitis C infection screening and care targeting PWIDs in Hai Phong, Vietnam**.

This model will encompass all steps involved in achieving HCV cure among individuals identified with hepatitis C:

i) Mass detection of PWIDs with hepatitis C;
ii) community-based support to improve referral to specific care;
iii) HCV simplified treatment delivered in hospital-based clinics;
iv) optimized treatment adherence;
v) harm reduction activities to encompass HCV transmission risk and prevention of HCV reinfection



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## PARTICIPATION IN THE STUDY

You have full freedom in accepting or refusing to participate in this project.

**If you refuse to participate in this study**, you will be proposed a referral to another hepatitis C specialist.

**If you accept to participate in this study**, you are invited to sign the consent form attached to this document that will also be signed by the medical doctor who offered you to participate in this study. You will also be offered to keep a copy of this form. **After signing the consent form**, you will undergo the pre-inclusion visit.

Women cannot participate in the study if they are pregnant. If it turns out that some conditions do not allow you to participate in the study, the medical doctor will explain the reasons and decide with you the most appropriate medical care.

## DETAILED FOLLOW-UP & TREATMENT

Around 1.050 patients will be enrolled in the study. The overall duration of the study will be 3 years.

Each patient will be followed up to 12 months after treatment initiation.

During the 12 months of this study, you will attend at least 9 visits with trained doctors in one of the 3 HCV clinics selected for the study, and get your blood checked at least 5 times for a total quantity of 68 ml in the entire study. This amount of blood sampling is not dangerous for your health at all.

During the whole study period, you can come to the hospital whenever you have any health problems, your doctor will suggest you undergo additional tests if needed.

For your safety, a Scientific Committee and an independent Data Safety and Monitoring Board will regularly meet to examine all new information related to the study (new data on treatment, new patient facts…) and monitor its correct implementation. They might decide to prematurely stop the study for safety reason.

**Visit 1 (Pre-inclusion visit):** During this visit, doctor and counselor will explain carefully all aspects of DRIVE-C study, and will answer your questions. Once enrolled in the study, an assessment of your health will be performed through a physical examination, blood tests, liver stiffness assessment, abdominal ultrasound and pregnancy test for women of childbearing age. Your blood will also be collected for the purpose of storage. You will be interviewed on your sexual and drug use behaviors (with focus on HCV infection risks) and on your quality of life. If you want, you will follow an HCV-related counseling session.

- If you present a severe associated disease requiring specific treatment or any clinical conditions, which might compromise the safety of HCV treatment, then you will not be proposed to initiate the HCV treatment.
- For woman: if you are pregnant or if you refuse to use a contraceptive method, then you will not be proposed to initiate the HCV treatment.

If you respond to all inclusion criteria, then you will be appointed within one to two week(s) for a second visit in the hepatitis clinic for initiating HCV treatment.

- If you are **co-infected with HIV** and **do not receive ART**, you will be offered to be referred to an OPC (outpatient clinic) for HIV care.
- If you are **co-infected with HBV** and require **treatment**, you will be offered to be referred to an specialist for HBV care.
- If you **do not receive MMT** (Methadone Maintenance Treatment), you will be offered to be referred to a methadone clinic for methadone initiation.
- In those cases, your second visit for initiating HCV treatment will be planned within 1 to 3 month(s) after starting ART, HBV treatment and/or methadone. The research staff will provide assistance and address all potential obstacles for you to enroll in care, including administrative issues.



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**Visit 2** (HCV treatment initiation): after clinical examination and before initiating the treatment, you will follow a session of therapeutic education including adherence counseling. You will receive a treatment for your hepatitis C based on the combination of two medicines already used in many countries, sofosbuvir and daclatasvir, that is highly efficient and recommended by the Vietnamese Ministry of Health for a total duration of 12 weeks.

The basic posology will be {one tablet of sofosbuvir 400-mg + one tablet of daclatasvir 60-mg} per day. For participants receiving efavirenz or nevirapine, daclatasvir dose will be adjusted to 90 mg/day.
In case of cirrhosis, ribavirin will be added to sofosbuvir/daclatasvir at a dose adapted to the patient weight (for patients < 75kg: 2 x 500 mg tablets per day). In case of ribavirin contra-indication, sofosbuvir-daclatasvir will be used for 24 weeks.

In order to ensure your safety during this study, you will be invited to return to the hepatitis clinic at 2, 4, 8, 12, 24, 36 and 48 weeks after the initiation of your treatment. You can return more frequently if you present any side effects of the treatment, if you have any questions about your health status or if you have any abnormal signs/symptoms.

By participating in the study, you agree to take the drugs according to the instructions provided by your study doctor and to come to the clinic for the scheduled study visits. For your own safety, you have to inform your study doctor about your health status and about all medicines, including prescription, over-the-counter (non-prescription), and herbal or alternative medicines you are taking. This is because there may be serious side-effects when other medicines are taken together with HCV treatment.

At week 2 (**Visit 3**), week 4 (**Visit** 4) and week 8 (**Visit 5**), you will benefit from a clinical check-up and treatment adherence support session. At Visit 4, biological check-up will be done again to confirm the tolerance of the HCV treatment and your blood will also be collected for the purpose of storage. No systematic blood test will be performed at Visit 3 and Visit 5, but doctor can ask if necessary. At visit 5, you will be interviewed on your sexual and drug use behaviors and on your quality of life.

At week 12 (**Visit 6**), corresponding to the end of treatment, you will undergo clinical examination, and HCV-related counseling session focusing on HCV re-infection risks. Your blood will be collected for the purpose of storage.

At week 24 (**Visit 7**), you will undergo clinical examination, interview on your sexual, drug use behaviors and your quality of life, and blood collection notably to assess the efficacy of HCV treatment by dosage of HCV virus circulating in blood. Your blood will also be collected for the purpose of storage, and you will undergo an HCV-related counseling session focusing on HCV re-infection risks.

At week 36 (**Visit 8**), you will undergo clinical examination and you will be informed if you are cured from HCV or not.

- If you are cured, you will undergo HCV-related counseling session where prevention of reinfection will be emphasized.
- If you are not cured, your doctor will assess the reasons of treatment failure. According to expert committee recommendations and drugs available in Vietnam, a new therapeutic plan could be proposed.

At week 48 (**Visit 9**), if you were cured at week 36, you will undergo clinical examination, interview and blood collection. You will be assessed for HCV re-infection. Your blood will also be collected for the purpose of storage, and you will undergo an HCV-related counseling session focusing on HCV re-infection risks.

For the success of the study, it is very important that you follow the visit schedule. If you cannot attend a visit, please inform your study doctor so that he/she can find another appointment with you. If you cannot attend a study visit and do not contact your study doctor, the study team will contact you by telephone or through the Community Based Organization worker who support you to know the reasons.

During the whole duration of the study, researchers may collect medical routine data about you in Hai Phong methadone programs and infectious disease clinics if you are participating in methadone treatment, HBV care or HIV care. They may also access and use your data collected within DRIVE study.

## POSSIBLE BENEFITS AND RISK/DISAVANTAGES OF TAKING PART

**What are the benefits of participating in this study?**

You will contribute to the answer of what is the best strategy to cure hepatitis C. It is a very important answer for all the PWIDs with chronic hepatitis C in Vietnam and in the whole world.

You will benefit from a new HCV treatment whatever the stage of your disease. The duration of the treatment is short. You will also benefit from thorough examinations to monitor your treatment, especially the HCV viral load in the blood, as well as access to HCV genotyping.

You will benefit from HCV-related counselling with respect to how you can protect your health and prevent being re-infected and from peer-support along the whole period of the study. The CBOs' members will assist you to address all potential obstacles to enrol in care, including administrative issues.

You will not pay any costs related to this study. The costs of the biological and radiological diagnosis, and hospitalization, if necessary, will be covered by the study.

Your participation is entirely voluntary and you will not receive any financial compensation except transportation expenses for all protocol visits.

**What are the possible risks of being in the study?**

HCV drugs can produce side-effects. The most common adverse events of these medications are: headache, fatigue, insomnia. Others can be: dizziness, migraine, nausea, diarrhea, abdominal pain, arthralgia or myalgia. Ribavirin added to sofosbuvir/daclatasvir for cirrhotic patients, can sometimes give anemia, decreased appetite, irritability, hot flush, dyspnea, dyspnea exertional, cough, nasal congestion, vomiting, gastroesophageal reflux disease, constipation, dry mouth, flatulence, rash, alopecia, pruritus or dry skin. Therefore, we will check for abnormalities in your blood during your follow-up visits. It is very important for you to be aware of it, and you will have to come back to see your doctor whenever you are sick so that the doctor can identify the cause of your illness and cure it.

Some people feel uncomfortable about being asked personal questions. Remember that you can refuse to answer any question that you do not want to. All information you provide for this study will be confidential.

Some people experience discomfort when blood is drawn and may feel dizzy or even faint. You may have a bruise or swelling where the needle goes into your arm. Some people may develop an infection where the needle goes into the arm, but this is very rare. In order to decrease this risk, our study nurses are well trained and qualified for the procedure.

The greatest risk may involve your privacy and confidentiality. We have considered this very carefully. Loss of confidentiality could cause other people to discriminate against you and could cause problems in your family and personal relationships. The steps to protect your privacy are described below.

## HOW WILL MY PRIVACY BE PROTECTED?

**What will happen to the information you give us?**

To protect your privacy, you will participate under a study code only, and your name will never appear in any study materials, blood samples, database or reports. Only codes will be used. The only study document with the name you provide to us and your code will be kept in a locked file at the hospital. Only study staff conducting the study and sponsor representatives can have access to your data and they are responsible for

your confidentiality. Any report or publication that results from this study will not use your name or identify you personally.

## HOW THE DATA IS PROCESSED?

As part of the study you may participate in, a treatment of your personal health data is implemented to analyze the results of the study with regard to the objectives.

The sponsor of the study, Inserm-ANRS, is a French research agency that fulfills a public interest mission. This justifies the processing of health data and data relative to (geographical origin, data relating to your sex life, etc.) for scientific research purposes, under European and French regulations.

In the event that your personal data are not collected directly from you, the source from which the data comes is your medical file.

The data processing will always be executed with guarantees of protection ensuring their confidentiality (use of a code).

**Data transfer**

Your data may be transferred to national or French or health authorities (drug agency ...), to other national or international private or public research teams. The data thus transmitted will be framed by appropriate and adapted guarantees provided in a contract / sharing agreement between Inserm-ANRS and the recipient (s) of the data under conditions guaranteeing the confidentiality of your data. Information on the purpose of the treatment through a newsletter will be sent to you at the appropriate time.

**Your rights:**

In accordance with the French law n ° 78-17 of 6 January 1978 amended in particular by Law 2018-493 of June 20, 2018, relating to Technology Data Files and Civil Liberties, you have a right to rectify your data collected, the right to oppose (right to opposition) or to limit their use (right to limitation of treatment).

Please note that in accordance with Article 17 of the General Data Protection Regulations (GDPR) to ensure compliance with Article L.1122-1-1 of the French Public Health Code, insofar as the erasure of data may make it impossible or seriously jeopardize the achievement of treatment goals, data collected prior to the withdrawal of your consent may not be erased and may continue to be processed under conditions that will ensure their minimization and confidentiality

You can also access, directly or through a doctor of your choice, all of your medical data in application of the provisions of Article L 1111-7 of the French Public Health Code.

The responsible of the data processing is the research sponsor (Inserm-ANRS) whose contact details are given on page 1 of this document.

If you have any questions regarding these rights or to obtain a copy of the contractual documents related to the transfer of your data, you can contact the doctor who will follow you in the course of the research.

In addition, the Data Protection Officer of Inserm is available for any question related to the processing of your data or the exercise of your rights by mail (dpo@inserm.fr) or by post (Delegate to data protection, INSERM, 101 rue de Tolbiac, 75013 Paris)

Finally, you have the right to lodge a complaint with the French supervisory authority: the CNIL (National Commission for Information Technology and Liberties).

Your data will be kept in accordance with current archiving regulations for clinical research.

## CAN I WITHDRAW FROM THE STUDY?

You can withdraw from this study whenever you wish. A last visit will then be done and your medical doctor will propose you a list of hepatitis C specialists to be referred to. Moreover, your participation in the study can be stopped by your doctor if s/he thinks it is necessary (to protect your safety or if you do not follow the research procedures). National Health Authorities or the Scientific Committee who monitors this study may also decide to end it.

Your doctor may stop prescribing you or changing you to another drug before the study ends if the continued use of research drugs can be harmful to you or if you cannot take study medication as prescribed in the protocol. If you must stop taking medication before the end of study, your doctor will recommend that you continue to participate in the study and return to the hospital for completion of all follow-up visits.

If you withdraw from the trial, you can express the will that your data be removed from the database and your laboratory samples be destroyed. If you do not express such will, data and samples collected prior to the date of your consent withdrawal could be used by the team.

## WHAT HAPPENS AT THE END OF THE TRIAL?

At the end of the study, the results will be disseminated to participants & PWID community through presentations and open discussions organized by the study's CBOs in their offices. At the end of the trial, you will be able to debrief with your study doctor about your participation and experience during the study. If you have cirrhosis, then your doctor will advise you about necessary regular follow-up with abdominal ultrasound for surveillance of liver cancer.

If you are cured, you will need to prevent from HCV reinfection, according to all information that were provided to you during the study counseling sessions.

## WHAT HAPPENS IF THERE IS A PROBLEM?

In case of problem, you should report it to your doctor.

For woman: if you become pregnant during the HCV treatment period, then you should inform your doctor. S/he will decide if the treatment must be discontinued for your fetus safety.

As sponsor, the Inserm-ANRS has taken an insurance policy which guarantees compensation if you experience any harm as a direct result of your involvement in this study.

## BIOLOGICAL SAMPLE STORAGE:

Some blood samples will be frozen for future HCV or drug use related research. Some analysis may not be available in Vietnam, therefore, blood samples may be sent overseas to accomplish additional researches. Providing your written consent, these samples will be kept anonymously in freezers in the laboratory of Hai Phong University of Medicine and Pharmacy. They will only be used for approved studies by Ethic Committees and regulatory authorities, in Vietnam or abroad. If genetic studies are planned with the stored blood, you will be asked again for your consent.

The expected duration of conservation is a maximum of 25 years.

The transfer of biological samples and data will be framed by appropriate safeguards and adapted provided in a contract / sharing agreement between the representative of Inserm-ANRS and the recipient (s) of the samples or data under conditions guaranteeing the confidentiality of your data.



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## CONTACT FOR FURTHER INFORMATION

During the study period, you can ask any question or request for additional information from your doctor or the person in charge of this study: Doctor PHAM Minh Khue (Hai Phong University of Medicine and Pharmacy). Phone number: 013 66 22 422

**ANRS N° 12380 DRIVE-C**

**Version n°1.0 of 27/04/2018 approved by HPMU IRB on 31/05/2018**

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**Declaration by Participant**

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- I have read or have been read the information notice attached with this form; I have understood the objective, advantages and disadvantages of the study, and the form is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurized to take part.
- I may choose to leave the study at any time and will not be penalized or prejudiced in any way.
- I accept that study team and any person involved in the study have access to my information according to the confidentiality rules.
- I accept that all confidential data collected for this study will be encoded and recorded in a computerized database.
- By signing this consent form, I have not waived any of the legal rights that I have as a participant in a research study.
- At the end of the study, I could be informed of the overall results of this research.
- I will be given a signed copy of this consent form and information sheet.

**I agree** to have my left over blood stored and tested for future research related to HCV, or other drug related diseases, in Vietnam or overseas:

Yes ☐ No ☐

**I agree** that the researchers may check with Hai Phong methadone programs and infectious disease clinics to see if I am participating in methadone treatment or HIV care and to collect medical routine data in the next 12 months. I also agree that they access and use my data collected within DRIVE study.

Yes ☐ No ☐

Signed at (*place*) ..... on (*date*) ..... 201_.

..... .....

Signature (or Thumbprint) of Participant Signature of Witness (if applicable)

**Declaration by the Investigator**

I *(name)* ..... declare that:

- I explained the information in this document to .....
- I encouraged the participant to ask questions and took adequate time to answer them.
- I am satisfied that the participant adequately understands all aspects of the research, as discussed above
- An interpreter was present during the information process: Yes ☐ No ☐

(*If an interpreter is used then the interpreter must sign the declaration below.)*

Signed at (*place*) ..... on (*date*) ..... 201_.

..... .....

Signature of Investigator Signature of interpreter (if applicable)



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