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Eliminating hepatitis C on the Balearic Islands, Spain: a protocol for an intervention study to test and link people who use drugs to care

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Eliminating hepatitis C on the Balearic Islands, Spain: a protocol for an intervention study to test and link people who use drugs to care

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Abstract (297/300 words)

Introduction: The hepatitis C virus (HCV) is a highly infectious and deadly disease, affecting some 58 million people worldwide. Of the 1.13 million people living in the Balearic Islands, Spain, about 1,350 individuals have untreated HCV. Of these, about 1,120 (83%) are estimated to be people who use drugs (PWUD), who are one of the key at-risk groups for HCV infection globally. Carrying out micro-elimination approaches focused on this population is crucial to achieve the World Health Organization (WHO) goal of eliminating HCV by 2030. Thus, the primary objective of this study is to validate a model of care that simplifies the screening and linkage to HCV care pathways for PWUD on the Balearic Islands.

Methods and analysis: This intervention study will be implemented across 17 sites, in four different settings: addiction service centres (n=12), non-governmental organisation centres (n=3), a mobile methadone unit, and a prison, with an estimated 3,725 participants. Together with the healthcare staff at each centre, the intervention protocols will be adapted, focusing on four phases: recruitment and testing; linkage to care; treatment for those who test positive; and monitoring of sustained virologic response 12 weeks after treatment and reinfection. The primary outcomes will be the number of tested and treated individuals and the secondary outcomes will include individuals lost at each step in the cascade of care. Descriptive analysis and multivariable logistic regression of the data will be undertaken.

Ethics and dissemination: The Hospital Clínic Barcelona, Spain ethics committee approved this study on 18 February 2021 (HCB/2020/2018). Findings will be disseminated through peer-reviewed publications, conference presentations, and social media. The results of this study could provide a model for targeting PWUD for HCV testing and treatment in the rest of Spain and in other settings, helping to achieve the WHO HCV elimination goal.

Strengths and limitations of this study

- This study is the first to address the elimination of hepatitis C virus (HCV) in the Balearic Islands, Spain.
- The study employs a micro-elimination model of care and telemedicine for prescribing treatment to simplify and expedite HCV diagnosis and care for people who use drugs (PWUD).
- This study's testing and treatment involves close collaboration with addiction service centres, a non-governmental organisation, a mobile methadone distributor, and a prison in the Balearic Islands in order to bring the services closer to marginalized populations.
- The study will also involve a motivational support programme for PWUD diagnosed with HCV so as to maximize retention in the cascade of care.
- This is a longitudinal study which, by nature, may experience loss to follow-up, which would reduce the number of participants and power of the data.

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INTRODUCTION

The hepatitis C virus (HCV) infection imposes a major disease burden globally, with untreated HCV potentially leading to hepatocellular carcinoma, liver cirrhosis, and death (1). An estimated 58 million people worldwide are living with HCV (2) and, in Spain, an estimated 0.22% of the general population (20-80 years) have an active HCV infection (3). One of the main problems in treating HCV is that a large proportion of the infected population is not aware of their status (4).

People who use drugs (PWUD) are one of the key at-risk groups for HCV infection globally. A systematic review of the prevalence of injecting drug use among people aged 15–64 years found that in most regions and countries, 52% (42-62%) of people who inject drugs (PWID, a sub-category of PWUD for the purposes of this protocol) were infected with HCV (5). Furthermore, a modelling study estimated that approximately 43% (25-67%) of new HCV infections may be prevented over the period of 2018–2030 if the increased risk for HCV transmission among PWID were removed (6). According to the Spanish Ministry of Health HCV Infection Screening Guide and the Observatory of Drugs and Addictions, in 2018 around 30% of the PWUD population infected with HCV was not aware of their status (3,7), making screening and treatment programmes crucial (8). Population-specific models need to be developed and implemented to simplify and facilitate access to testing, treatment, and prevention services for marginalized groups such as PWUD. These models will also allow for taking advantage of synergies between health care services and other organisations addressing substance use (9,10). Furthermore, because the "test and treat" strategy is cost-effective for HCV screening and because HCV can be easily cured with direct-acting antivirals (DAAs), the long-term consequences and spread of the disease can be prevented, making it possible to achieve the WHO global HCV elimination goal by 2030 (8).

In order to reduce the HCV burden among PWUD, strategies such as the micro-elimination approach should facilitate targeted interventions (11). In addition, it has been shown that the decentralization of HCV care and its integration in harm reduction centres improves access to diagnosis, linkage to care, and treatment (12). Such strategies or models of care have been tested elsewhere, e.g., in Gipuzkoa, Spain, where a care pathway for PWID to facilitate HCV diagnosis and elimination was implemented in methadone dispensing treatment centres. In this study, about 80% of the population with an active infection was treated (13). In Italy, micro-elimination efforts for PWUD were conducted in addiction care centres, identifying those infected, initiating DAA treatment, and carrying out follow-up monitoring after treatment completion (14). In southern Italy, an HCV screening and treatment programme was carried out in PWUD in addiction centres and a university hospital, which found that 42% of participants had an active HCV infection and that almost half of them were unaware of their status (15). Also in Italy, a testing and treatment programme carried out in several prisons focused on PWID found that this population was less likely to be aware of their HCV positive status and to have been previously treated and most participants (>80%) in this study underwent treatment (16). A 2019 review examined which strategies can improve HCV screening and diagnosis, and found that the point-of-care (PoC) and dried blood spot (DBS) tests are valuable tools for large-scale HCV detection, diagnosis, and treatment, leading to an improvement in healthcare accessibility (17).

DAAs can cure ≥95% of people with HCV, but there is insufficient screening of hepatitis C infection and consequently treatment rates remain low (5). Even though as a whole Spain is on track to meet the

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WHO elimination targets by 2030 (18), and improving early diagnosis and access to treatment for HCV is a goal of its National Strategy on Addictions (19), many of the country's 17 autonomous communities (regions) do not test and treat enough (3) in spite of the country's national viral hepatitis strategy, in place since May 2015 (20), and unrestricted access to DAA treatment since June 2017 (21).

The autonomous community of the Balearic Islands, Spain, which includes the islands of Mallorca, Menorca, Ibiza, and Formentera, has a total population of 1.13 million and an estimated 1,350 individuals living with untreated HCV infection, according to the HCV prevalence data of the Spanish Ministry of Health (20). Of this population, an estimated 1,120 (83%) are PWUD. The size of the Balearic Islands and the proximity of the three major islands to each other makes this an ideal setting for a study that will greatly accelerate the elimination of HCV among PWUD in this part of Spain.

Making the testing and linkage-to-care pathway easier for patients to navigate is an essential strategy to achieve the WHO goal of eliminating HCV as a major public health threat by 2030 (22). Health system and other barriers deter many HCV-infected PWUD from obtaining care at hospitals (23,24), creating a need to engage them in other settings. Research has shown that PWUD are receptive to receiving HCV screening at addiction service centres (25), but a lack of resources, infrastructure, clear care pathways, and expertise prevent many of these facilities from performing HCV screening. Even when screening takes place, HCV-infected PWUD typically present late for care (26,27). PWUD are also often lost to follow-up (LTFU) before they have undergone confirmatory HCV testing and received additional care. An example of a missed opportunity for HCV diagnosis and linkage to care is a programme that delivers methadone via a mobile van to some 100 people every day across the island of Mallorca, which does not provide HCV testing to patients. Another example in the Balearic Islands' is that prisoners, which include a large number of PWUD, are tested for HCV immediately upon entering the penal system, but HCV-infected prisoners who subsequently are released on bail are commonly LTFU before they can be linked to care in the community. In both examples, telemedicine, one aspect of simplification that this project will introduce, could improve the situation (28,29).

A study of this scale has never been conducted on the Balearic Islands. This project will create new care pathways and leverage existing ones to scale up the currently limited and dispersed efforts to treat HCV among PWUD on the Balearic Islands by catalysing coordination among key stakeholders. Findings from the programmatic models under investigation can inform the use of simplified HCV test-and-link-to-care strategies in other parts of Spain and abroad in line with the Spanish Viral Hepatitis Elimination Coalition's recommendations (30) as well as the EASL International Liver Foundation's micro-elimination approach (11) to HCV elimination worldwide.

The main aim of this study is to validate a model of care that simplifies the screening and linkage to HCV care pathways for PWUD on the Balearic Islands by following a micro-elimination strategy to reduce the HCV prevalence in this population by improving diagnostic rates and treatment and reducing the number of current and new infections.

METHODS AND ANALYSIS

Study design and setting

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This is a prospective cohort study using implementation science methods, which aims to validate a model of care that simplifies the screening and linkage to care and measure the prevalence of HCV infection among PWUD on the Balearic Islands. The study will be implemented at 17 sites, in four different settings with large PWUD populations: addiction centres ("Unidad de Conductas Adictivas", UCAs) (Figure 1), non-governmental organisation (NGO) centres ("Projecte Home Balears") (Figure 1), a mobile methadone unit ("Metabús") (Figure 2), and a Mallorca prison (Figure 3). The expected number of PWUD participating in the study, including all the study centres, is 3,725 (Table 1).

Addiction centres: The UCAs are outpatient centres for people dealing with addiction to various substances and/or addictive behaviours and their families. They consist of multidisciplinary teams (doctors, nurses, psychologists, and social workers). There is a total of 12 UCAs serving adults on the Balearic Islands. Of these, nine are located on the island of Mallorca and include four UCAs managed by the primary health care system (IBSalut) and five managed by the Counsel of Mallorca. Menorca has two UCAs managed by the Counsel of Menorca and Ibiza has one UCA managed by the Counsel of Ibiza. Across all three islands, the UCAs serve an estimated 3,325 patients who are at risk of HCV infection. HCV testing is not regularly carried out at the UCAs.

NGO centres: Projecte Home's mission is to prevent, treat, and respond to issues generated by addictions in society. It does so through individual and group interventions adapted for some 300 people affected by addiction and their families across all three islands. All three main centres, located in Mallorca, Menorca, and Ibiza, are included as study sites. HCV testing has never been carried out here before.

Mobile methadone unit: The Metabús distributes methadone in Palma, Mallorca. It is run by the Red Cross, an NGO operating on the island. Every day of the year, the Metabús makes five stops, twice a day, throughout Palma to distribute methadone to some 100 patients who have been prescribed it by one of the UCAs in Palma. HCV testing has never been carried out in this setting.

Mallorca prison: This is the largest prison in the Balearic Islands, located in Palma, and receives inmates from the other islands. This prison currently houses 1,100 inmates and another 156 individuals who are in preventive custody. PWUD among the preventive custody population is the focus of our study at this site. The prison doctor is committed to establishing a care pathway that connects prisoners in preventive custody to HCV care, which is currently not the case.

The study will have four sequential phases or interventions. First, participants will be offered a PoC anti-HCV antibody (Ab) test (OraQuick® rapid PoC test). Second, if they test positive for the anti-HCV Ab-test, they will be offered a blood analysis with fibrosis indicators (aspartate transaminase to platelet ratio index (APRI) and Fibrosis 4 scores (FIB-4)) or a DBS to test for viremia (HCV-RNA). In both cases, blood analysis and DBS, there will also be testing for HIV and HBV. If they are HCV-RNA positive, DAA treatment will be offered, prescribed via telemedicine by a hepatologist and dispensed at the study site where the participant is followed. Finally, after 12 weeks after treatment a DBS to confirm cure and sustained virologic response 12 weeks after treatment (SVR12) will be offered and, if they continue with high-risk behaviours, a DBS test to monitor for reinfection will be offered 12 months after SVR12.

Patient or public involvement

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Patients were not involved in the planning of this study. There was, however, public involvement in the planning of this study via agreement to participate and coordination with the study sites. There is an official agreement between the Balearic Islands Health Service (IBSalut) and the Barcelona Institute for Global Health (ISGlobal), which is leading the project, for collaboration and data transfer, with the aim of facilitating the exchange of information and so that the tests carried out and their results are recorded in the official health history of the patients. Additionally, this collaboration contributes to the sustainability of HCV elimination efforts once the project ends.

Study population

The study will be conducted on PWUD, recruited in Mallorca, Menorca, and Ibiza from UCAs, Projecte Home Balears, the Metabús, and a prison; participants must have a self-reported history of drug use (active or former), be 18 years of age or older, and provide informed consent.

Subjects will not be eligible to enrol in the study if they are unable to understand written or verbal instructions in Spanish, Catalan, or English or any other language used by the health care providers or if they are currently receiving treatment for HCV.

Statistical analysis and sample size justification

This is an observational, descriptive study. It is therefore not possible to make a power calculation. However, there are an estimated 1,350 individuals with HCV viremia in the Balearic Islands. This study will offer an HCV diagnosis to the estimated 3,725 PWUD (Table 1) attending the 17 study sites during one full year.

Descriptive statistics (e.g., demographics, epidemiology of HCV infection, history of drug use, previous testing and outcomes) collected at baseline will be used to describe participant demographic characteristics. All categorical measures will be summarised using frequency and proportions (in percentages). Continuous variables will be described using the following statistics: mean, standard deviation, median, minimum, and maximum. 95% confidence intervals will be estimated for proportions and means. The prevalence of HCV infection and HCV cascade of care (CoC) will be calculated for the whole sample and stratified according to the following categories: gender, age, country of origin, and study setting.

To assess the risk factors related to HCV infection as well as completion of each major step on the HCV CoC (RNA confirmatory test, treatment initiation, treatment success (defined as completion of the CoC steps and reaching SVR12 or a proxy [e.g., sustained virologic response (SVR) 4 weeks after treatment or end of treatment response (EoT)]), and reinfection rate), multivariable logistic regression models to calculate odds ratios and their 95% confidence intervals will be performed using a stepwise forward approach (including all of the variables that in the bivariate analysis show a p-value of <0.20 and through review of the literature to include relevant covariates for the exposure variables of interest). The significance level will be set to <0.05 and data will be analysed using STATA (version 14.0).

Study period

The study will be implemented during a 30-month period from 29th March 2021, after a delayed October 2020 start, due to COVID-19 pandemic restrictions in Spain, which restricted movement and use of the healthcare system.

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After meeting with all participating centres, adaptation of the intervention protocols for each study setting will be carried out (months 1-4). The recruitment phase will take place in all 17 setting centres during months 5-16, during which time data collection will take place in addition to data management on a rolling basis. Treatment prescription and initiation of those diagnosed in the recruitment phase and follow-up of participants will be carried out during the recruitment phase and in months 17-22. The final analysis will be carried out during months 23-27, when all participants who tested positive for HCV antibodies will have completed the cascade of care or will have been LTFU. These five months will also be used for data purification and final quality control.

Study outcomes

The primary outcomes for this study will be the number of tested and treated individuals and the prevalence of those infected by HCV among the PWUD population of the Balearic Islands. The prevalence of HCV infection will be calculated for the whole sample and stratified according to the following categories: gender, age, country of origin, and study setting.

Secondary outcomes will include descriptive analysis of the study population in each of the four settings, including anti-HCV Ab and HCV-RNA prevalence; time from positive anti-HCV Ab test to HCV-RNA confirmation; proportion that initiated and completed treatment; time from HCV confirmatory diagnosis by RNA evaluation until DAA initiation rates; and reasons for LTFU along the HCV care cascade.

Basic demographics (e.g., age, gender, education level, employment status, housing), brief drug history (e.g., ever enrolled in drug treatment), and mode of reported HCV transmission will be considered in order to describe the study population in each of the study settings. Finally, the number of patients with SVR at EoT and 12 weeks after EoT as well as any cases of re-infection will be reported.

Testing procedures

Testing and diagnosis: All study participants (apart from those in the prison) will be tested for anti-HCV Ab via the OraQuick® rapid PoC test, which uses oral fluid rather than blood. If positive, they will be referred for a confirmatory test at a nearby health centre. If they prefer not to go to the centre, they will be offered DBS testing at the study site which will then be transported to the central laboratory to confirm viremia. Participants in the prison setting will follow the already established screening process in the prison. Those who meet bail and leave prison custody before receiving their results will be contacted through the new created model.

Linkage to care: We will implement simplified care pathways to facilitate linkage to care. This will include study coordinator visits to the 12 UCAs (n=~2,390 patients already in care and an estimated 935 new individuals each year), the three Projecte Home Balears main centres (n=~300), and the Metabús (n=~100). Linkage to care at the prison (n=~200), will be managed by prison staff with support from the study coordinator.

Treatment: DAAs will be prescribed via telemedicine, when relevant, after confirmatory HCV-RNA testing. The choice of DAA therapy will be set in accordance with the standard of care set out in national guidelines and will take into consideration possible drug-drug interactions. The study

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coordinator will deliver the prescribed DAAs from the hospital pharmacy to the study site (except for the prison setting).

Monitoring for reinfection: DBS testing will be utilized to monitor for reinfection 12 months after achieving SVR (n=~225). This number is based on the estimated number of patients who will have initiated treatment in the first three months of the recruitment phase.

Referral and follow-up

In the case of positive HCV-RNA results, patients will be informed during their follow-up visit of their diagnosis and all patients who agree to be treated will receive telematic treatment prescription and DAAs on site, delivered by the study coordinator after agreement with the patient. For those with a blood draw, APRI and FIB-4 scores for fibrosis stage will be calculated. In the instance that APRI and FIB-4 scores indicate significant fibrosis, patients will be referred to the hospital for follow-up and care by the hepatologist. If patients have no signs of significant fibrosis, they will be followed-up at the UCA/Projecte Home centre. Patients initiating treatment during the first three months of recruitment will be monitored for re-infection via DBS testing after 12 months by the centre (UCA, Projecte Home Balears, or Metabús) staff.

In the prison, in the case of positive HCV-RNA results, health care personnel will refer the patient to a study centre or hospital for care. Continued monitoring will be done at the centre of choice and if the person returns to prison while still under care, they will be linked to the existing care pathway in the prison system in order to complete treatment. Re-infection control for this setting will not be part of this study because of the guidelines in place which indicate that all persons who enter the prison will have a venous blood draw performed.

Obtaining and using biological samples

Participation in this study involves obtaining a sample (either saliva or whole blood). Anti-HCV Ab will be screened through a single-use OraQuick® rapid PoC test. Anti-HCV Ab positive tests will be referred to a nearby health centre to undergo a venous blood extraction or DBS test in order to perform HCV-RNA testing to confirm active infection. The DBS test will be offered and performed onsite, which entails 350µl of blood, and will be sent to the central laboratory for reflex testing. Samples will be obtained and used in accordance with the provisions of Law 14/2007 on biomedical research and Royal Decree 1716/2011, which regulates the use of biological samples in research. By signing the informed consent form, which will be available in Spanish, Catalan, and English**,** participants agree to allow members of the research team the use of the obtained samples that will be obtained for the purposes of this study exclusively.

Biological samples used for the OraQuick® rapid PoC test will be performed and analysed on-site by the study coordinator and the centre staff in the respective community setting and samples will be disposed of immediately after their use following proper biological material disposal protocols and destroyed.

Analysis of all biological samples performed via DBS and venous blood extraction will be done in the Molecular Microbiology Units of the two reference hospitals in the Balearic Islands (Son Espases

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University Hospital and Son Llàtzer University Hospital). Biological samples will be destroyed after their use.

Treatment for HCV

Treatment will be prescribed via telemedicine by the corresponding hepatologist who will choose the most appropriate pangenomic DAA for the patient. Treatment will be collected at the hospital pharmacies by the study coordinator, always with the prior authorization of the patient, and will be taken to the study centres. Treatment will be dispensed at the study centre corresponding to each patient and, depending on the characteristics of the patient and the opinion of the centre staff, it will be dispensed more or less frequently (e.g., daily, weekly, biweekly, monthly, along with methadone, etc.). Records of the dispensation of and adherence to treatment will be carried out in each study centre.

Data collection and management

Data will be collected at each step of the cascade of care: testing (anti-HCV Ab and HCV-RNA), delivery of results and linkage to care, treatment initiation, treatment completion, SVR12 status, and 12 months after SVR12 to monitor for reinfection**.** By collecting data at each step of the cascade of care, patient drop-off along the cascade of care will also be monitored.

The project implementer (typically the study coordinator) at all study sites will collect data from study participants using a Microsoft Excel template. Each Microsoft Excel record that is completed will be individually purified by a project/data manager at ISGlobal to unify and merge with the master Microsoft Excel database. All variables will be recoded to ensure consistency and accuracy and will be recorded in a STATA 14.0 codebook. No personal identifying information will be passed onto the Excel files for analysis.

Descriptive statistics (e.g., sociodemographic characteristics, epidemiology of HCV infection, previous testing) and outcomes collected at baseline will be used to describe participant demographic characteristics.

Data will be compiled and reviewed to quality check for inconsistencies or possible reporting errors. All categorical measures will be summarised using frequency and proportions (%). Continuous variables will be described using the following statistics: mean, standard deviation, median, minimum, and maximum. 95% confidence intervals will be estimated for proportions and means. Results will be presented in tables, including any missing observations.

ETHICS AND DISSEMINATION

This study complies with national and international laws and regulations on ethical issues (Law 14/2007 of July 3 of Biomedical Research; Declaration of Helsinki and Tokyo but adapted to the current regulations). The confidentiality of the persons and their data is guaranteed, according to the European Union Regulation 2016/679 of the European Parliament and the Council of April 27, 2016 on the protection of persons with regard to the processing of personal data and the free circulation of data, being binding as of May 25, 2018. All participants will be informed verbally and in writing of their participation in a research study. The project, along with the informed consent forms, was approved

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by the ethics committee of the Hospital Clínic, Barcelona, Spain (HCB/2020/2018). Informed consent forms for patients include: introduction, note on voluntary participation, general description of the study, benefits and risks of participation, confidentiality, and obtaining and using biological samples.

Additionally, participants will be informed that the personal information collected will only be utilised for the sole purposes described in the protocol. Contact information (e.g., telephone numbers and/or emails) will be collected to follow-up with patients who will be referred for specialist care and for those who require DAA therapy. Participants will be able to participate even if they do not consent to providing their contact information.

To ensure the continuation of care after the end of the project, educational programmes will be carried out on the different procedures (OraQuick® rapid PoC test, DBS, follow-up adherence to treatment, SVR12, and reinfection control) for the staff of the participating centres. Requests for rapid PoC tests and their results will also be incorporated into the medical records of participating patients, so that it is recorded in the Balearic Islands Health System records.

Findings will be disseminated through peer-reviewed publications, conference presentations, and social media.

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Authors' contributions

JVL, MB, and AV conceived of the project. JVL, CAP, and MV-R drafted the project protocol with input from MB, AV, and AH. AH drafted the first iteration of this manuscript with assistance from MV-R and JVL. All authors reviewed the full draft of the article, subsequent revisions and approved the final version for submission.

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Competing interest statement

JVL reports grants, personal fees, and other from AbbVie and Gilead Sciences, personal fees from CEPHEID, GSK, Intercept, and Janssen, and grants and personal fees from MSD, outside the submitted work. MB reports advisory fees from Gilead Sciences, Abbvie, GlaxoSmithKline, and Assembly Biosciences and speaker fees from Gilead Sciences and Abbvie, outside of the submitted work. AV, AH, CAP, MV-R, AR, JMA, AM, AP, ET, and FB have no competing interest to declare.

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Table 1: Estimation of sample to be tested by island and setting based on latest data available.

	UCA (n=12)	**Projecte Home Balears** (n=3)	**Metabús** (n=1)
Mallorca	900 patients with high-risk behaviour, plus an additional 900 on OST	200	100 regular users (75 fixed, 25 varying)
Menorca	200 patients with high-risk behaviour, plus an additional 90 on OST	50	N/A
Ibiza	150 patients with high-risk behaviour, plus an additional 150 on OST	50	N/A
An estimated 935 individuals enter the addiction centres for the first time every year.			
Total estimated PWUD to be tested for HCV as part of the study: 3,725			

Abbreviations: HCV, hepatitis C virus; OST, opioid substitution therapy; PWUD, people who use drugs; UCA, ("Unidad de Conductas Adictivas", addiction service centre).

Note: The prison setting is not included in the calculation. The estimated 156 patients in preventive care there are tested as part of the prison standard of care.

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Figure 1. UCAs and Projecte Home Balears study setting.

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Figure 2. Mobile methadone unit ("Metabús") study setting.

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Figure 3. Mallorca prison study setting.

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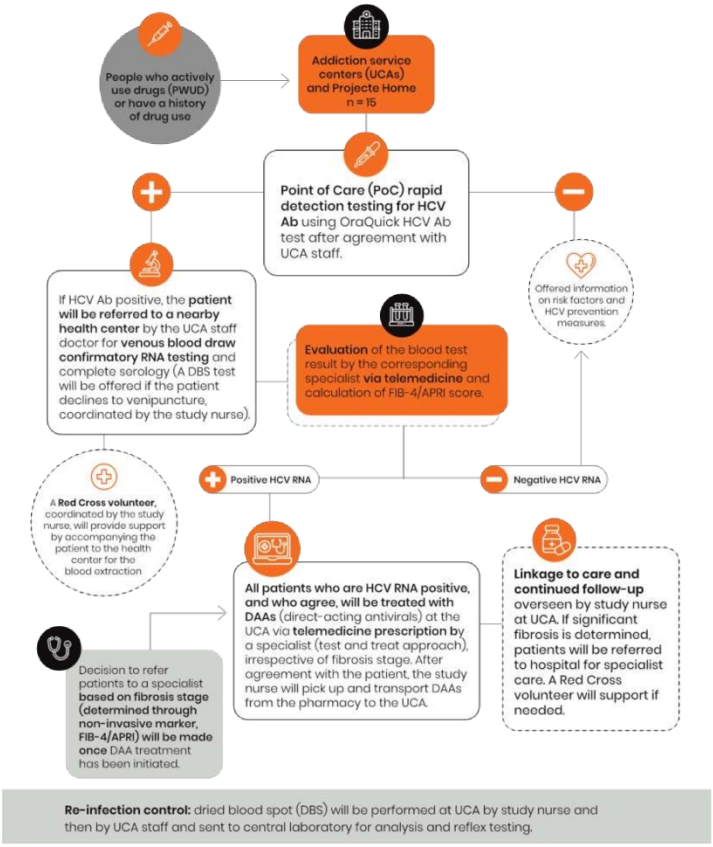
Figure 1. UCAs and Projecte Home Balears study setting.



Abbreviations: Ab, antibody; APRI, aspartate transaminase to platelet ratio index; FIB-4, Fibrosis 4; HCV, hepatitis C virus.

Figure 1. UCAs and Projecte Home Balears study setting.

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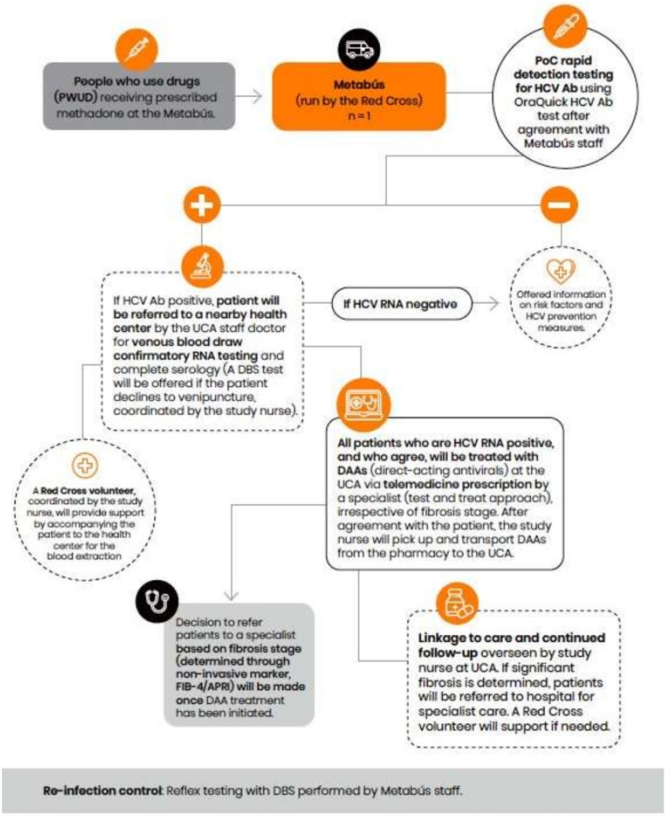
Figure 2. Mobile methadone unit ("Metabús") study setting.

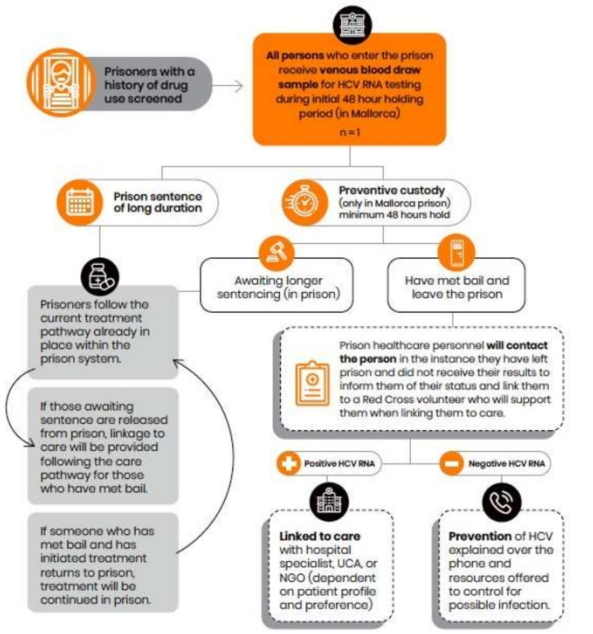


Abbreviations: APRI, aspartate transaminase to platelet ratio index; DBS, dried blood spot; FIB-4, Fibrosis 4; HCV, hepatitis C virus; PoC, point-of-care; UCA, ("Unidad de Conductas Adictivas", addiction service centre).

Figure 2. Mobile methadone unit ("Metabús") study setting.

215x279mm (300 x 300 DPI)

Figure 3. Mallorca prison study setting.



Abbreviations: HCV, hepatitis C virus; NGO, non-governmental organisation; UCA, ("Unidad de Conductas Adictivas", addiction service centre).
Note: Due to COVID-19 pandemic measures, HCV-RNA testing takes longer than the 48 hours reported in the figure.

Figure 3. Mallorca prison study setting.

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Eliminating hepatitis C on the Balearic Islands, Spain: a protocol for an intervention study to test and link people who use drugs to care

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Abstract (297/300 words)

Introduction: The hepatitis C virus (HCV) is a highly infectious and deadly disease, affecting some 58 million people worldwide. Of the 1.13 million people living in the Balearic Islands, Spain, about 1,350 individuals have untreated HCV. Of these, about 1,120 (83%) are estimated to be people who use drugs (PWUD), who are one of the key at-risk groups for HCV infection globally. Carrying out micro-elimination approaches focused on this population is crucial to achieve the World Health Organization (WHO) goal of eliminating HCV by 2030. Thus, the primary objective of this study is to validate a model of care that simplifies the screening and linkage to HCV care pathways for PWUD on the Balearic Islands.

Methods and analysis: This intervention study will be implemented across 17 sites, in four different settings: addiction service centres (n=12), non-governmental organisation centres (n=3), a mobile methadone unit, and a prison, with an estimated 3,725 participants. Together with the healthcare staff at each centre, the intervention protocols will be adapted, focusing on four phases: recruitment and testing; linkage to care; treatment for those who test positive; and monitoring of sustained virologic response 12 weeks after treatment and reinfection. The primary outcomes will be the number of tested and treated individuals and the secondary outcomes will include individuals lost at each step in the cascade of care. Descriptive analysis and multivariable logistic regression of the data will be undertaken.

Ethics and dissemination: The Hospital Clínic Barcelona, Spain ethics committee approved this study on 18 February 2021 (HCB/2020/2018). Findings will be disseminated through peer-reviewed publications, conference presentations, and social media. The results of this study could provide a model for targeting PWUD for HCV testing and treatment in the rest of Spain and in other settings, helping to achieve the WHO HCV elimination goal.

Strengths and limitations of this study

- This study is the first to address the elimination of hepatitis C virus (HCV) in the Balearic Islands, Spain.
- The study employs a micro-elimination model of care and telemedicine for prescribing treatment to simplify and expedite HCV diagnosis and care for people who use drugs (PWUD).
- This study's testing and treatment involves close collaboration with addiction service centres, a non-governmental organisation, a mobile methadone distributor, and a prison in the Balearic Islands in order to bring the services closer to marginalized populations.
- The study will also involve a motivational support programme for PWUD diagnosed with HCV so as to maximize retention in the cascade of care.
- This is a longitudinal study which, by nature, may experience loss to follow-up, which would reduce the number of participants and power of the data.

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INTRODUCTION

The hepatitis C virus (HCV) infection imposes a major disease burden globally, with untreated HCV potentially leading to hepatocellular carcinoma, liver cirrhosis, and death (1). An estimated 58 million people worldwide are living with HCV (2) and, in Spain, an estimated 0.22% of the general population (20-80 years) have an active HCV infection (3). One of the main problems in treating HCV is that a large proportion of the infected population is not aware of their status (4).

People who use drugs (PWUD) are one of the key at-risk groups for HCV infection globally. A systematic review of the prevalence of injecting drug use among people aged 15–64 years found that in most regions and countries, 52% (42-62%) of people who inject drugs (PWID, a sub-category of PWUD for the purposes of this protocol) were infected with HCV (5). Furthermore, a modelling study estimated that approximately 43% (25-67%) of new HCV infections may be prevented over the period of 2018–2030 if the increased risk for HCV transmission among PWID were removed (6). According to the Spanish Ministry of Health HCV Infection Screening Guide and the Observatory of Drugs and Addictions, in 2018 around 30% of the PWUD population infected with HCV was not aware of their status (3,7), making screening and treatment programmes crucial (8). Population-specific models need to be developed and implemented to simplify and facilitate access to testing, treatment, and prevention services for marginalized groups such as PWUD. These models will also allow for taking advantage of synergies between health care services and other organisations addressing substance use (9,10). Furthermore, because the "test and treat" strategy is cost-effective for HCV screening and because HCV can be easily cured with direct-acting antivirals (DAAs), the long-term consequences and spread of the disease can be prevented, making it possible to achieve the WHO global HCV elimination goal by 2030 (8).

In order to reduce the HCV burden among PWUD, strategies such as the micro-elimination approach should facilitate targeted interventions (11). In addition, it has been shown that the decentralization of HCV care and its integration in harm reduction centres improves access to diagnosis, linkage to care, and treatment (12). Such strategies or models of care have been tested elsewhere, e.g., in Gipuzkoa, Spain, where a care pathway for PWID to facilitate HCV diagnosis and elimination was implemented in methadone dispensing treatment centres. In this study, about 80% of the population with an active infection was treated (13). In Italy, micro-elimination efforts for PWUD were conducted in addiction care centres, identifying those infected, initiating DAA treatment, and carrying out follow-up monitoring after treatment completion (14). In southern Italy, an HCV screening and treatment programme was carried out in PWUD in addiction centres and a university hospital, which found that 42% of participants had an active HCV infection and that almost half of them were unaware of their status (15). Also in Italy, a testing and treatment programme carried out in several prisons focused on PWID found that this population was less likely to be aware of their HCV positive status and to have been previously treated and most participants (>80%) in this study underwent treatment (16). A 2019 review examined which strategies can improve HCV screening and diagnosis, and found that the point-of-care (PoC) and dried blood spot (DBS) tests are valuable tools for large-scale HCV detection, diagnosis, and treatment, leading to an improvement in healthcare accessibility (17).

DAAs can cure ≥95% of people with HCV, but there is insufficient screening of hepatitis C infection and consequently treatment rates remain low (5). Even though as a whole Spain is on track to meet the

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WHO elimination targets by 2030 (18), and improving early diagnosis and access to treatment for HCV is a goal of its National Strategy on Addictions (19), many of the country's 17 autonomous communities (regions) do not test and treat enough people (3) in spite of the country's national viral hepatitis strategy, in place since May 2015 (20), and unrestricted access to DAA therapy since June 2017 (21).

The autonomous community of the Balearic Islands, Spain, which includes the islands of Mallorca, Menorca, Ibiza, and Formentera, has a total population of 1.13 million and an estimated 1,350 individuals living with untreated HCV infection, according to the HCV prevalence data of the Spanish Ministry of Health (20). Of this population, an estimated 1,120 (83%) are PWUD. The size of the Balearic Islands and the proximity of the three major islands to each other makes this an ideal setting for a study that will greatly accelerate the elimination of HCV among PWUD in this part of Spain.

Making the testing and linkage-to-care pathway easier for patients to navigate is an essential strategy to achieve the WHO goal of eliminating HCV as a major public health threat by 2030 (22). Health system and other barriers deter many HCV-infected PWUD from obtaining care at hospitals (23,24), creating a need to engage them in other settings. Research has shown that PWUD are receptive to receiving HCV screening at addiction service centres (25), but a lack of resources, infrastructure, clear care pathways, and expertise prevent many of these facilities from performing HCV screening. Even when screening takes place, HCV-infected PWUD typically present late for care (26,27). PWUD are also often lost to follow-up (LTFU) before they have undergone confirmatory HCV testing and received additional care. An example of a missed opportunity for HCV diagnosis and linkage to care is a programme that delivers methadone via a mobile van to some 100 people every day across the island of Mallorca, which does not provide HCV testing to patients. Another example in the Balearic Islands' is that prisoners, which include a large number of PWUD, are tested for HCV immediately upon entering the penal system, but HCV-infected prisoners who subsequently are released on bail are commonly LTFU before they can be linked to care in the community. In both examples, telemedicine, one aspect of simplification that this project will introduce, could improve the situation (28,29).

A study of this scale has never been conducted on the Balearic Islands. This project will create new care pathways and leverage existing ones to scale up the currently limited and dispersed efforts to treat HCV among PWUD on the Balearic Islands by catalysing coordination among key stakeholders. Findings from the programmatic models under investigation can inform the use of simplified HCV test-and-link-to-care strategies in other parts of Spain and abroad in line with the Spanish Viral Hepatitis Elimination Coalition's recommendations (30) as well as the EASL International Liver Foundation's micro-elimination approach (11) to HCV elimination worldwide.

The main aim of this study is to validate a model of care that simplifies the screening and linkage to HCV care pathways for PWUD on the Balearic Islands by following a micro-elimination strategy to reduce the HCV prevalence in this population by improving diagnostic rates and treatment and reducing the number of current and new infections.

METHODS AND ANALYSIS

Study design and setting

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This is a prospective cohort study using implementation science methods, which aims to validate a model of care that simplifies the screening and linkage to care and measure the prevalence of HCV infection among PWUD on the Balearic Islands. The study will be implemented at 17 sites, in four different settings with large PWUD populations: addiction centres ("Unidad de Conductas Adictivas", UCAs) (Figure 1), non-governmental organisation (NGO) centres ("Projecte Home Balears") (Figure 1), a mobile methadone unit ("Metabús") (Figure 2), and a Mallorca prison (Figure 3). The expected number of PWUD participating in the study, including all the study centres, is 3,725 (Table 1).

Addiction centres: The UCAs are outpatient centres for people dealing with addiction to various substances and/or addictive behaviours and their families. They consist of multidisciplinary teams (doctors, nurses, psychologists, and social workers). There is a total of 12 UCAs serving adults on the Balearic Islands. Of these, nine are located on the island of Mallorca and include four UCAs managed by the primary health care system (IBSalut) and five managed by the Counsel of Mallorca. Menorca has two UCAs managed by the Counsel of Menorca and Ibiza has one UCA managed by the Counsel of Ibiza. Across all three islands, the UCAs serve an estimated 3,325 patients who are at risk of HCV infection. HCV testing is not regularly carried out at the UCAs.

NGO centres: Projecte Home's mission is to prevent, treat, and respond to issues generated by addictions in society. It does so through individual and group interventions adapted for some 300 people affected by addiction and their families across all three islands. All three main centres, located in Mallorca, Menorca, and Ibiza, are included as study sites. HCV testing has never been carried out here before.

Mobile methadone unit: The Metabús distributes methadone in Palma, Mallorca. It is run by the Red Cross, an NGO operating on the island. Every day of the year, the Metabús makes five stops, twice a day, throughout Palma to distribute methadone to some 100 patients who have been prescribed it by one of the UCAs in Palma. HCV testing has never been carried out in this setting.

Mallorca prison: This is the largest prison in the Balearic Islands, located in Palma, and receives inmates from the other islands. This prison currently houses 1,100 inmates and another 156 individuals who are in preventive custody. PWUD among the preventive custody population is the focus of our study at this site. The prison doctor is committed to establishing a care pathway that connects prisoners in preventive custody to HCV care, which is currently not the case.

The study will have four sequential phases or interventions. First, participants will be offered a PoC anti-HCV antibody (Ab) test (OraQuick® rapid PoC test). Second, if they test positive with the anti-HCV Ab-test, they will be offered a blood analysis with fibrosis indicators (aspartate transaminase to platelet ratio index (APRI) and Fibrosis 4 scores (FIB-4)) or a DBS to test for viremia (HCV-RNA). In both cases, blood analysis and DBS, there will also be testing for HIV and HBV. If they are HCV-RNA positive, DAA treatment will be offered, prescribed via telemedicine by a hepatologist and dispensed at the study site where the participant is followed. Finally, after 12 weeks after treatment a DBS to confirm cure and sustained virologic response 12 weeks after treatment (SVR12) will be offered and, if they continue with high-risk behaviours, a DBS test to monitor for reinfection will be offered 12 months after SVR12.

Patient or public involvement

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Patients were not directly involved in the planning of this study. There was, however, public involvement in the planning of this study via agreement to participate and coordination with the study sites. There is an official agreement between the Balearic Islands Health Service (IBSalut) and the Barcelona Institute for Global Health (ISGlobal), which is leading the project, for collaboration and data transfer, with the aim of facilitating the exchange of information and so that the tests carried out and their results are recorded in the official health history of the patients. Additionally, this collaboration contributes to the sustainability of HCV elimination efforts once the project ends.

Study population

The study will be conducted with PWUD recruited in Mallorca, Menorca, and Ibiza from UCAs, Projecte Home Balears, the Metabús, and a prison; participants must have a self-reported history of drug use (active or former), be 18 years of age or older, and provide informed consent.

Subjects will not be eligible to enrol in the study if they are unable to understand written or verbal instructions in Spanish, Catalan, or English or any other language used by the health care providers or if they are currently receiving treatment for HCV.

Statistical analysis and sample size justification

This is an observational, descriptive study. It is therefore not possible to make a power calculation. However, there are an estimated 1,350 individuals with HCV viremia in the Balearic Islands. This study will offer an HCV diagnosis to the estimated 3,725 PWUD (Table 1) attending the 17 study sites during one full year.

Descriptive statistics (e.g., demographics, epidemiology of HCV infection, history of drug use, previous testing and outcomes) collected at baseline will be used to describe participant demographic characteristics. All categorical measures will be summarised using frequency and proportions (in percentages). Continuous variables will be described using the following statistics: mean, standard deviation, median, minimum, and maximum. 95% confidence intervals will be estimated for proportions and means. The prevalence of HCV infection and HCV cascade of care (CoC) will be calculated for the whole sample and stratified according to the following categories: gender, age, country of origin, and study setting.

To assess the risk factors related to HCV infection as well as completion of each major step on the HCV CoC (RNA confirmatory test, treatment initiation, treatment success (defined as completion of the CoC steps and reaching SVR12 or a proxy [e.g., sustained virologic response (SVR) 4 weeks after treatment or end of treatment response (EoT)]), and reinfection rate), multivariable logistic regression models to calculate odds ratios and their 95% confidence intervals will be performed using a stepwise forward approach (including all of the variables that in the bivariate analysis show a p-value of <0.20 and through review of the literature to include relevant covariates for the exposure variables of interest). The significance level will be set to <0.05 and data will be analysed using STATA (version 14.0).

Study period

The study will be implemented during a 30-month period from 29th March 2021, after a delayed October 2020 start, due to COVID-19 pandemic restrictions in Spain, which restricted movement and use of the healthcare system.

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After meeting with all participating centres, adaptation of the intervention protocols for each study setting will be carried out (months 1-4). The recruitment phase will take place in all 17 setting centres during months 5-16, during which time data collection will take place in addition to data management on a rolling basis. Treatment prescription and initiation of those diagnosed in the recruitment phase and follow-up of participants will be carried out during the recruitment phase and in months 17-22. The final analysis will be carried out during months 23-27, when all participants who tested positive for HCV antibodies will have completed the cascade of care or will have been LTFU. These five months will also be used for data purification and final quality control.

Study outcomes

The primary outcomes for this study will be the number of tested and treated individuals and the prevalence of those infected by HCV among the PWUD population of the Balearic Islands. The prevalence of HCV infection will be calculated for the whole sample and stratified according to the following categories: gender, age, country of origin, and study setting.

Secondary outcomes will include descriptive analysis of the study population in each of the four settings, including anti-HCV Ab and HCV-RNA prevalence; time from positive anti-HCV Ab test to HCV-RNA confirmation; proportion that initiated and completed treatment; time from HCV confirmatory diagnosis by RNA evaluation until DAA initiation rates; and reasons for LTFU along the HCV care cascade.

Basic demographics (e.g., age, gender, education level, employment status, housing), brief drug history (e.g., ever enrolled in drug treatment), and mode of reported HCV transmission will be considered in order to describe the study population in each of the study settings. Finally, the number of patients with SVR at EoT and 12 weeks after EoT as well as any cases of re-infection will be reported.

Testing procedures

Testing and diagnosis: All study participants (apart from those in the prison) will be tested for anti-HCV Ab via the OraQuick® rapid PoC test, which uses oral fluid rather than blood. If positive, they will be referred for a confirmatory test at a nearby health centre. If they prefer not to go to the centre, they will be offered DBS testing at the study site which will then be transported to the central laboratory to confirm viremia. Participants in the prison setting will follow the already established screening process in the prison. Those who meet bail and leave prison custody before receiving their results will be contacted through the new created model.

Linkage to care: We will implement simplified care pathways to facilitate linkage to care. This will include study coordinator visits to the 12 UCAs (n=~2,390 patients already in care and an estimated 935 new individuals each year), the three Projecte Home Balears main centres (n=~300), and the Metabús (n=~100). Linkage to care at the prison (n=~200), will be managed by prison staff with support from the study coordinator.

Treatment: DAAs will be prescribed via telemedicine, when relevant, after confirmatory HCV-RNA testing. The choice of DAA therapy will be set in accordance with the standard of care set out in national guidelines and will take into consideration possible drug-drug interactions. The study

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coordinator will deliver the prescribed DAAs from the hospital pharmacy to the study site (except for the prison setting).

Monitoring for reinfection: DBS testing will be utilized to monitor for reinfection 12 months after achieving SVR (n=~225). This number is based on the estimated number of patients who will have initiated treatment in the first three months of the recruitment phase.

Referral and follow-up

In the case of positive HCV-RNA results, patients will be informed during their follow-up visit of their diagnosis and all patients who agree to be treated will receive telematic treatment prescription and DAAs on site, delivered by the study coordinator after agreement with the patient. For those with a blood draw, APRI and FIB-4 scores for fibrosis stage will be calculated. In the instance that APRI and FIB-4 scores indicate significant fibrosis, patients will be referred to the hospital for follow-up and care by the hepatologist. If patients have no signs of significant fibrosis, they will be followed-up at the UCA/Projecte Home centre. Patients initiating treatment during the first three months of recruitment will be monitored for re-infection via DBS testing after 12 months by the centre (UCA, Projecte Home Balears, or Metabús) staff.

In the prison, in the case of positive HCV-RNA results, health care personnel will refer the patient to a study centre or hospital for care. Continued monitoring will be done at the centre of choice and if the person returns to prison while still under care, they will be linked to the existing care pathway in the prison system in order to complete treatment. Re-infection control for this setting will not be part of this study because of the guidelines in place which indicate that all persons who enter the prison will have a venous blood draw performed.

Obtaining and using biological samples

Participation in this study involves obtaining a sample (either saliva or whole blood). Anti-HCV Ab will be screened through a single-use OraQuick® rapid PoC test. Anti-HCV Ab positive tests will be referred to a nearby health centre to undergo a venous blood extraction or DBS test in order to perform HCV-RNA testing to confirm active infection. The DBS test will be offered and performed onsite, which entails 350µl of blood, and will be sent to the central laboratory for reflex testing. Samples will be obtained and used in accordance with the provisions of Law 14/2007 on biomedical research and Royal Decree 1716/2011, which regulates the use of biological samples in research. By signing the informed consent form, which will be available in Spanish, Catalan, and English**,** participants agree to allow members of the research team the use of the obtained samples that will be obtained for the purposes of this study exclusively.

Biological samples used for the OraQuick® rapid PoC test will be performed and analysed on-site by the study coordinator and the centre staff in the respective community setting and samples will be disposed of immediately after their use following proper biological material disposal protocols and destroyed.

Analysis of all biological samples performed via DBS and venous blood extraction will be done in the Molecular Microbiology Units of the two reference hospitals in the Balearic Islands (Son Espases

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University Hospital and Son Llàtzer University Hospital). Biological samples will be destroyed after their use.

Treatment for HCV

Treatment will be prescribed via telemedicine by the corresponding hepatologist who will choose the most appropriate pangenomic DAA for the patient. Treatment will be collected at the hospital pharmacies by the study coordinator, always with the prior authorization of the patient, and will be taken to the study centres. Treatment will be dispensed at the study centre corresponding to each patient and, depending on the characteristics of the patient and the opinion of the centre staff, it will be dispensed more or less frequently (e.g., daily, weekly, biweekly, monthly, along with methadone, etc.). Records of the dispensation of and adherence to treatment will be carried out in each study centre.

Data collection and management

Data will be collected at each step of the cascade of care: testing (anti-HCV Ab and HCV-RNA), delivery of results and linkage to care, treatment initiation, treatment completion, SVR12 status, and 12 months after SVR12 to monitor for reinfection**.** By collecting data at each step of the cascade of care, patient drop-off along the cascade of care will also be monitored.

The project implementer (typically the study coordinator) at all study sites will collect data from study participants using a Microsoft Excel template. Each Microsoft Excel record that is completed will be individually purified by a project/data manager at ISGlobal to unify and merge with the master Microsoft Excel database. All variables will be recoded to ensure consistency and accuracy and will be recorded in a STATA 14.0 codebook. No personal identifying information will be passed onto the Excel files for analysis.

Descriptive statistics (e.g., sociodemographic characteristics, epidemiology of HCV infection, previous testing) and outcomes collected at baseline will be used to describe participant demographic characteristics.

Data will be compiled and reviewed to quality check for inconsistencies or possible reporting errors. All categorical measures will be summarised using frequency and proportions (%). Continuous variables will be described using the following statistics: mean, standard deviation, median, minimum, and maximum. 95% confidence intervals will be estimated for proportions and means. Results will be presented in tables, including any missing observations.

ETHICS AND DISSEMINATION

This study complies with national and international laws and regulations on ethical issues (Law 14/2007 of July 3 of Biomedical Research; Declaration of Helsinki and Tokyo but adapted to the current regulations). The confidentiality of the persons and their data is guaranteed, according to the European Union Regulation 2016/679 of the European Parliament and the Council of April 27, 2016 on the protection of persons with regard to the processing of personal data and the free circulation of data, being binding as of May 25, 2018. All participants will be informed verbally and in writing of their participation in a research study. The project, along with the informed consent forms, was approved

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by the ethics committee of the Hospital Clínic, Barcelona, Spain (HCB/2020/2018). Informed consent forms for patients include: introduction, note on voluntary participation, general description of the study, benefits and risks of participation, confidentiality, and obtaining and using biological samples.

Additionally, participants will be informed that the personal information collected will only be utilised for the sole purposes described in the protocol. Contact information (e.g., telephone numbers and/or emails) will be collected to follow-up with patients who will be referred for specialist care and for those who require DAA therapy. Participants will be able to participate even if they do not consent to providing their contact information.

To ensure the continuation of care after the end of the project, educational programmes will be carried out on the different procedures (OraQuick® rapid PoC test, DBS, follow-up adherence to treatment, SVR12, and reinfection control) for the staff of the participating centres. Requests for rapid PoC tests and their results will also be incorporated into the medical records of participating patients, so that it is recorded in the Balearic Islands Health System records.

Findings will be disseminated through peer-reviewed publications, conference presentations, and social media.

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Authors' contributions

JVL, MB, and AV conceived of the project. JVL, CAP, and MV-R drafted the project protocol with input from MB, AV, and AH. AH drafted the first iteration of this manuscript with assistance from MV-R and JVL. All authors (JVL, AH, CAP, MV-R, AR, JMA, AM, AP, ET, FB, MB, and AV) reviewed the full draft of the article, subsequent revisions and approved the final version for submission.

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Competing interest statement

JVL reports grants, personal fees, and other from AbbVie and Gilead Sciences, personal fees from CEPHEID, GSK, Intercept, and Janssen, and grants and personal fees from MSD, outside the submitted work. MB reports advisory fees from Gilead Sciences, Abbvie, GlaxoSmithKline, and Assembly Biosciences and speaker fees from Gilead Sciences and Abbvie, outside of the submitted work. AV, AH, CAP, MV-R, AR, JMA, AM, AP, ET, and FB have no competing interest to declare.

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Table 1: Estimation of sample to be tested by island and setting based on latest data available.

	UCA (n=12)	**Projecte Home Balears** (n=3)	**Metabús** (n=1)
Mallorca	900 patients with high-risk behaviour, plus an additional 900 on OST	200	100 regular users (75 fixed, 25 varying)
Menorca	200 patients with high-risk behaviour, plus an additional 90 on OST	50	N/A
Ibiza	150 patients with high-risk behaviour, plus an additional 150 on OST	50	N/A
An estimated 935 individuals enter the addiction centres for the first time every year.			
Total estimated PWUD to be tested for HCV as part of the study: 3,725			

Abbreviations: HCV, hepatitis C virus; OST, opioid substitution therapy; PWUD, people who use drugs; UCA, ("Unidad de Conductas Adictivas", addiction service centre).

Note: The prison setting is not included in the calculation. The estimated 156 patients in preventive care there are tested as part of the prison standard of care.

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Figure 1. UCAs and Projecte Home Balears study setting.

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Figure 2. Mobile methadone unit ("Metabús") study setting.

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Figure 3. Mallorca prison study setting.

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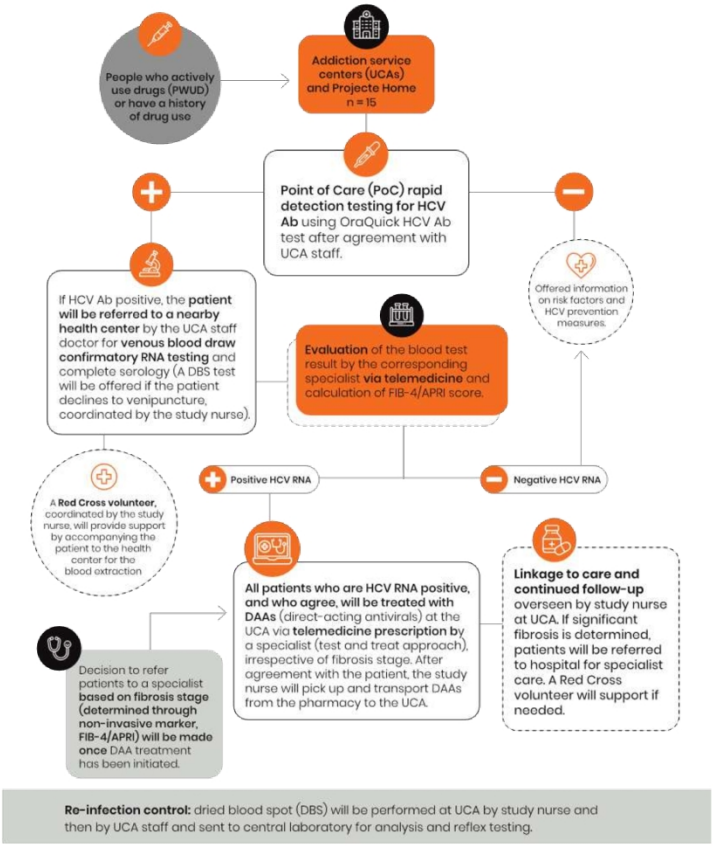
Figure 1. UCAs and Projecte Home Balears study setting.



Abbreviations: Ab, antibody; APRI, aspartate transaminase to platelet ratio index; FIB-4, Fibrosis 4; HCV, hepatitis C virus.

Figure 1. UCAs and Projecte Home Balears study setting.

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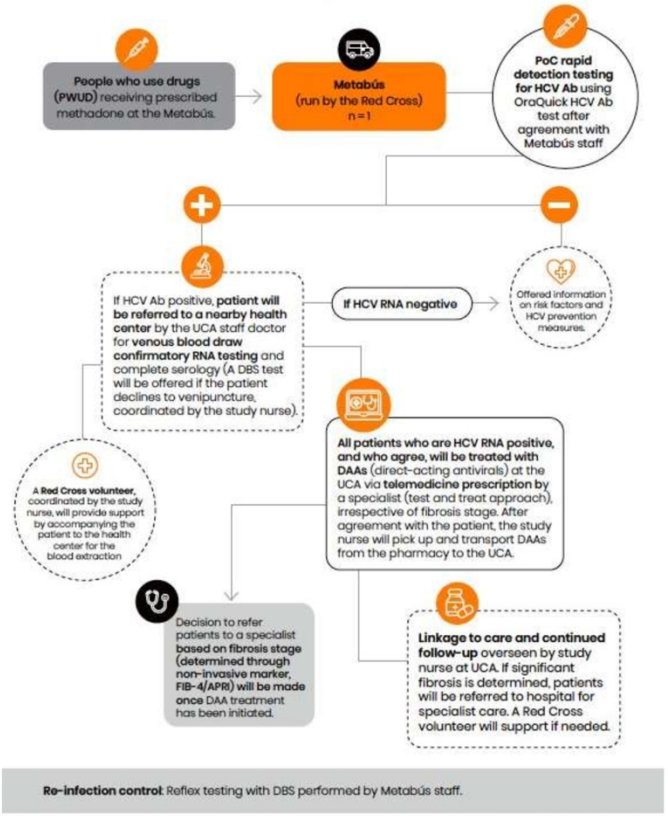
Figure 2. Mobile methadone unit ("Metabús") study setting.



Abbreviations: APRI, aspartate transaminase to platelet ratio index; DBS, dried blood spot; FIB-4, Fibrosis 4; HCV, hepatitis C virus; PoC, point-of-care; UCA, ("Unidad de Conductas Adictivas", addiction service centre).

Figure 2. Mobile methadone unit ("Metabús") study setting.

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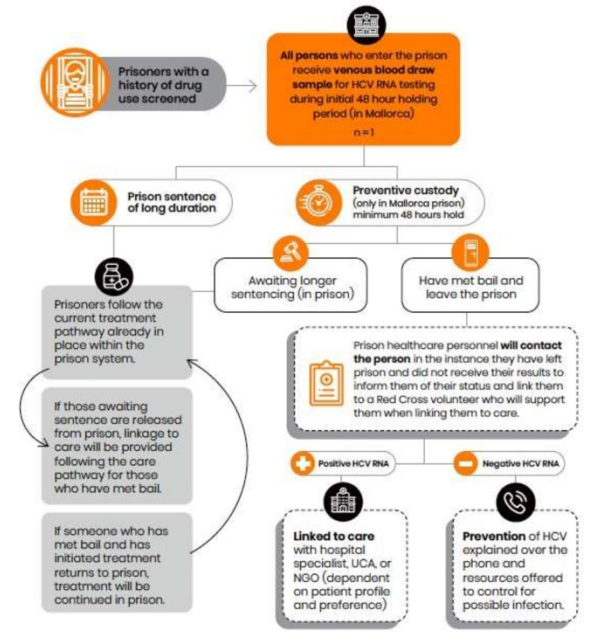
Figure 3. Mallorca prison study setting.



Abbreviations: HCV, hepatitis C virus; NGO, non-governmental organisation; UCA, ("Unidad de Conductas Adictivas", addiction service centre).
Note: Due to COVID-19 pandemic measures, HCV-RNA testing takes longer than the 48 hours reported in the figure.

Figure 3. Mallorca prison study setting.

209x297mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **(done in the title and abstract, p 2)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **(NA, protocol)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **(done, p 3-4)**
Objectives	3	State specific objectives, including any prespecified hypotheses **(done, p 4)**
Methods		
Study design	4	Present key elements of study design early in the paper **(done, p 5)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **(done, p 5-9)**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **(done, p 6 and 8)**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **(NA)**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **(done, p 7)**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **(done, p 7-9)**
Bias	9	Describe any efforts to address potential sources of bias **(NA, protocol)**
Study size	10	Explain how the study size was arrived at **(done, p 6)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **(done, p 9)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **(done, p 9)**
		(*b*) Describe any methods used to examine subgroups and interactions **(NA)**
		(*c*) Explain how missing data were addressed **(NA, protocol)**
		(*d*) If applicable, explain how loss to follow-up was addressed **(NA, protocol)**
		(*e*) Describe any sensitivity analyses **(NA, protocol)**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility,

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		confirmed eligible, included in the study, completing follow-up, and analysed **(NA, protocol)**
		(b) Give reasons for non-participation at each stage **(NA, protocol)**
		(c) Consider use of a flow diagram **(NA, protocol)**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **(NA, protocol)**
		(b) Indicate number of participants with missing data for each variable of interest **(NA, protocol)**
		(c) Summarise follow-up time (eg, average and total amount) **(NA, protocol)**
Outcome data	15*	Report numbers of outcome events or summary measures over time **(NA)**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **(NA, protocol)**
		(*b*) Report category boundaries when continuous variables were categorized **(NA, protocol)**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **(NA, protocol)**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **(NA, protocol)**
Discussion		
Key results	18	Summarise key results with reference to study objectives **(NA, protocol)**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **(done, p 2)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **(NA, protocol)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **(NA, protocol)**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **(done, p 12)**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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