# UK Cohort for Acute Hepatitis C: A prospective, multicentre, observational, cohort study of Acute Hepatitis C in the United Kingdom

# UKACH

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| Professor Graham Cooke | 26th November 2020 |  |

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## Funder

The trial is supported in by an award from the National Institute of Healthcare Research (NIHR, UK)

This protocol describes the UKACH study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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## GLOSSARY OF ABBREVIATIONS

| | |
|---|---|
| **AE** | Adverse event |
| **AR** | Adverse reaction |
| **ART** | Antiretroviral therapy |
| **ARV** | Antiretroviral |
| **CF** | Consent Form |
| **CI** | Chief Investigator |
| **CI** | Confidence interval |
| **COM** | Clinical Operations Manager |
| **CPA, CPB, CPC** | Child's Pugh (classification) A, B, C |
| **CPM** | Clinical Project Manager |
| **CRF** | Case Report Form |
| **CTU** | Clinical Trials Unit |
| **DAA** | Direct Acting Antiviral |
| **DCV** | Daclatasvir |
| **DCF** | Data Clarification Form |
| **DM** | Data Manager |
| **DMC** | Data Monitoring Committee |
| **DNA** | Deoxyribonucleic acid |
| **EASL** | European Association for Study of Liver |
| **EC** | Ethics Committtee |
| **ELISA** | Enzyme linked immuno absorbent assay |
| **ELISPOT** | Enzyme linked immuno absorbent spot |
| **EOT** | End of treatment |
| **FDA** | (US) Food and Drug Administration |
| **GCP** | Good Clinical Practice |
| **HCV** | Hepatitis C Virus |
| **HIV** | Human Immunodeficiency Virus |
| **ICH** | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| **IRB** | Institutional Review Board |
| **LLOQ** | Lower level of quantification |
| **LMIC** | Lower and middle income countries |

| | |
|---|---|
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **MRC** | Medical Research Council |
| **NGS** | Next generation sequencing |
| **NIMP** | Non-investigational-medicinal product |
| **OD** | Once daily |
| **PI** | Principal Investigator |
| **PIS** | Patient Information Sheet |
| **PREP** | Pre Exposure Prophylaxis |
| **PWID** | People Who Inject Drugs |
| **QoL** | Quality of life |
| **QP** | Qualified Person |
| **R&D** | Research and Development |
| **RAS** | Resistance Associated Substitution |
| **RCT** | Randomised controlled trial |
| **REC** | Research Ethics Committee |
| **RNA** | Ribonucleic acid |
| **SAE** | Serious adverse event |
| **SAR** | Serious adverse reaction |
| **SOF** | Sofosbuvir |
| **SOP** | Standard operating procedure |
| **SVR** | Sustained virological response (persistently undetectable) |
| **TMG** | Trial Management Group |
| **VL** | Viral load |
| **WGS** | Whole Genome Sequencing |
| **WHO** | World Health Organization |

## KEYWORDS

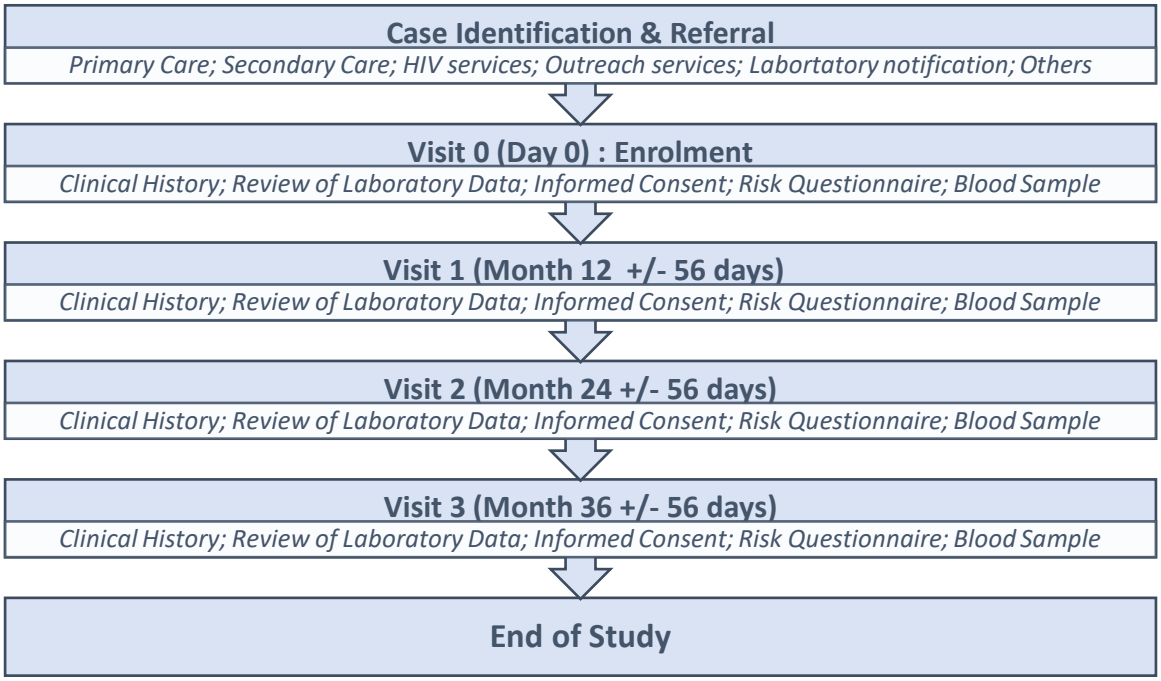
Hepatitis C; HCV; Human Immunodeficiency virus; HIV; Injection drug use; IDU; Person who injects drugs; PWID; MSM

## STUDY SUMMARY

| | |
|---|---|
| **TITLE** | UK Acute Cohort Hepatitis C |
| **ACRONYM** | UKACH |
| **DESIGN** | Prospective, observational, multi-centre cohort study |
| | |
| **PRIMARY OBJECTIVE** | • To identify and describe cases of acute HCV infection in the United Kingdom |
| | |
| **PRIMARY OUTCOME MEASURES** | • Descriptive statistics (n[%]) relating to participant characteristics (demographics and risk factors) and virus characteristics (genotype) at baseline and during follow up. |
| **SECONDARY OBJECTIVES** | • To describe risk factors for acute HCV that are amenable for prevention.<br>• To describe response to direct-acting antiviral treatment in the context of acute infection.<br>• To identify networks of ongoing transmission of HCV<br>• To describe the rate of re-infection following successful treatment of acute HCV<br>• To describe linkage to care and treatment in those with acute infection<br>• To perform a phylogenetic analysis of HCV transmission |
| **SECONDARY OUTCOME MEASURES** | • Descriptive statistics of risk factors collectively and by individual acquisition risk sub-groups, including but not limited to MSM, PWID, primary infection and re-infection. Analysis will be performed at baseline and at at timepoints 12, 24 and 36 months of follow-up.<br>• Proportion on patients with acute infection with an undetectable viral load at 3 years post enrolment; SVR at 12 weeks post completion of DAA treatment; SVR at 24 weeks post completion of DAA treatment; Treatment regimens and source (NHSE, clinical trial, self-sourced via internet); Analysis will be performed overall and by acquisition risk sub-group (including but not limited to MSM, PWID, primary infection and re-infection).<br>• Descriptive network analysis including clustering and geographic analysis based upon epidemiological data.<br>• Proportion of individuals meeting criteria for re-infection at month 12, 24 and 36 of follow up, collectively and by individual |

| | |
|---|---|
| | subgroup. Time to event analysis using Kaplan-Meir method from time since achieving sustained virological response.<br>• Proportion of cases under ongoing secondary care follow up defined as attending annual follow up visits in secondary care; Proportion of cases discharged from routine follow up owing to successful treatment; Proportion lost to follow up. Data summarised at timepoints 12, 24 and 36 months of follow-up.<br>• Phylogentic analysis using whole genome sequencing of HCV isolates; Maximum likelihood phylogenetic trees; Clustering analysis; Time to most recent common ancestor. |
| **Exploratory Objectives** | • To describe the characteristics and magnitude of the HCV reservoir in peripheral blood mononuclear cells in patients with acute hepatitis C infection.<br>• To describe the host immune response to HCV in acute infection |
| **Exploratory Outcome Measures** | • PCR and sequencing of HCV virus from sorted peripheral blood mononuclear cells.<br>• Exploratory immunological assays of HCV-specific humoral and cellular responses, including but not limited to ELISA, ELISPOT and flow cytometry. |
| **POPULATION** | Adults (aged =>18 years) with acute hepatitis C (HCV) infection |
| **ELIGIBILITY** | Evidence of acute hepatits C infection or re-infection defined:<br>I. A positive HCV RNA test in the presence of a negative anti-HCV test (antibody and/or antigen and/or HCV RNA) within the past 12 months<br>II. A positive HCV RNA test with an acute clincial hepatitis (jaundice or ALT rise >5x ULN) and no other identifiable cause;<br>III. A positive HCV RNA test in patients who had previously achieved spontaneous clearance (anti-HCV positive individuals with two consecutive negative HCV RNA results 24 weeks apart and did not receive treatment), sustained virological response following treatment (negative HCV RNA result 24 (for IFN-based) or 12 weeks (DAA), after stopping treatment or later.<br>IV. Evidence of HCV genotype and/or sub-type switch |
| **PARTICIPANT FOLLOW UP** | Annually for 3 years after initial recruitment |
| **DURATION** | 3 years |

## REFERENCE DIAGRAM



| | Visit 0 *(Day 0)* | Visit 1 *(Month 12 +/- 56days)* | Visit 2 *(Month 24 +/- 56days)* | Visit 3 *(Month 36 +/- 56days)* |
|---|---|---|---|---|
| **Informed consent** | X | | | |
| **Continued consent** | | X | X | X |
| **Medical History[A]** | X | X | X | X |
| **Review Laboratory Parameters** | X | X | X | X |
| **Questionnaire** | X | X | X | X |
| **Blood sample[B]** | X | X | X | X |

***Table 1 – Study schedule.*** *A participant information booklet will be provided on, or prior to, the first study visit. Participants will be given the opportunity to ask any questions regarding the study. A repeat consent form (continued consent) will be collected at subsequent study visits (V1-V3) to ensure ongoing consent for participation. A – Medical history will consist of active ongoing symptoms, pre-existing medical conditions at enrolment, medication history (including allergies) and family history. The medical history will be updated at subsequent study visits and recorded in the case record file; B – Blood samples will be collected only in those participants who provide explicit consent.*

# 1. INTRODUCTION

## 1.1 Background

Hepatitis C (HCV) remains a major cause of morbidity and mortality throughout the world, responsible for approximately 600,000 deaths in 2015, the great majority from liver cancer and cirrhosis (Stanaway et al., 2016). Previous interferon-based treatments required prolonged treatment, had significant toxicity and were often ineffective in curing hepatitis C. In recent years, interferon-free treatments for HCV with directly acting antivirals (DAAs) have made highly effective and tolerable treatment more widely accessible to patients. Interferon based therapy was a particular challenge for HIV positive patients who had lower sustained virologic responses rates (SVR) compared to that seen in HIV negative individuals, a difference no longer seen with DAA therapy (Sikavi et al., 2018).

The transformation in HCV treatment has contributed to ambitious World Health Organisation (WHO) targets for elimination of HCV as a public health threat by 2030, including a 90% reduction in new HCV infections. Achieving these targets will require substantial effort and investment a part of a broad elimination strategy and require targeting groups at high risk of ongoing transmission (Cooke et al., 2019) (Heffernan et al., 2019a). As part of such strategies, the concept of micro-elimination has been proposed to break down wider population elimination targets into those focussed on smaller subgroups for more targeted efforts (Lazarus et al., 2017). Measuring ongoing acute infection is a major barrier to using these targets in public health responses.

### 1.1.1 Acute HCV Infection – Assessing Incidence in the UK

Globally there are an estimated 1.75 million acute HCV infections each year, very few of these are symptomatic or recognised clinically (Cooke et al., 2019), measuring ongoing new infection is therefore a major challenge in monitoring the impact of prevention and treatment services. The Public Health England annual report recognises the challenge of diagnosing acute infection and uses three metrics (i) an estimate of incidence in PWID (ii) prevalence of anti-HCV Ab among those recently initiating IDU treatment programmes and (iii) prevalence of anti-HCV Ab in young adults (the last two being proxy measures). There was no evidence for a decline in incidence in PWID, based on data from the unlinked anonymous monitoring (UAM) survey of PWID in contact with specialist services between 2011-2017 (estimated incidence approximately 200/1000PYFU in 2017). The numbers of individuals recently starting injection with available data is small but suggests no change in recent years. There is some reduction in the proportion of young adults testing positive for hepatitis C, though the relevance of this is unclear. Taken together there is little evidence of a change in HCV incidence yet in PHE figures.

In Scotland, recent transmission of hepatitis C is captured through the NESI (Needle Exchange Surveillance Initiative) Survey of PWID, identifying those who are HCV Ab negative but have detectable virus (Mcauley et al., 2019). Data from Scotland up to 2015 suggest a slight increase in awareness of HCV infection over this period, though this may not suggest a change in underlying incidence of infection. Although Indicator 1 for the Scottish BBV framework is the reduction in recently acquired HCV infections, there are no data available in the most recent report.

HIV positive MSM are a key risk group for ongoing acute hepatitis C infection. Reflecting experience from other European cohorts, data presented in 2019 suggest a decline in acute HCV infections of approximately 68% (from 17.7 to 4.6 per 100 person years of follow up [PYFU]) across a number of large HIV treatment centres in the UK (see later for more details). This is likely to reflect improved

access to treatment for those at risk of transmitting infection and earlier access to treatment, but still falls short of the 90% WHO target.

There are benefits to the individual in early identification and diagnosis of acute hepatitis C infection. Individuals may be offered treatment if their infection is not spontaneously resolving and treatment with DAA therapy has high success rates in the acute setting, potentially requiring short courses of therapy to achieve cure.

Modelling studies suggest that ongoing transmission from those who are acutely infected has an important role in driving the HCV epidemic (Popping et al., 2019) (Heffernan et al., 2019b) (Cooke et al., 2019). Early diagnosis and linkage to care is therefore important in preventing ongoing transmission. As the majority of acute HCV infection are asymptomatic, identifying and diagnosing newly acquired HCV infection remains a challenge -- including in relatively developed healthcare settings such as the UK. Consequently, there are very little data on epidemiology of acute HCV infections within the UK (PHE, 2019). The available data that exist are derived from the HIV-HCV co-infected population, which suggest there have been significant reduction in the time from acute infection to initiation of DAA treatment (PHE, 2018). However but there are limited data available for other at-risk populations including PWID (Trickey et al., 2019).

### 1.1.2 High-risk populations for acute HCV infection in the UK

The key at-risk populations for acute infections are well recognised in the UK (PHE, 2019). These may be defined by behaviour including Injecting drug users, sexually active men who have sex with men (MSM) and, less commonly, individuals exposed in healthcare settings. Alternatively, they may be defined by their locations including HIV services, in-patients' services, the vulnerably housed and those on remand/in prison.

#### 1.1.2.1 Acute infection HIV positive and HIV negative MSM populations

The HIV positive MSM population is possibly the best characterised of those at ongoing risk of HCV infection. Previous work in the UK HIV population suggests over 90% of acute HCV infections affect a small proportion of individuals with high-risk behaviours for HCV transmission, including both sexual behaviours, illicit drug use and the combination of both "chemsex" (Martin et al., 2016).

Early modelling studies predicted that substantial scale up of access to DAA therapy had the potential to reduce the prevalence of chronic infection in HIV positive MSM by over 70% by 2025 (Martin et al., 2016) (Martin et al., 2013). Real world experience in other countries has suggested that such declines in HCV infection in HIV positive MSM can be seen where treatment access is good (Boerekamps, Newsum, et al., 2018) (Boerekamps, van den Berk, et al., 2018). However, a reduction in new HCV infections depends on a number of factors, including the extent to which those with active infection are engaged in care, the frequency of screening of at-risk populations and access to highly effective DAA treatment. Declines in acute HCV infection have not been observed in all settings (Boerekamps, Newsum, et al., 2018)(Pradat et al., 2018) (Sulkowski, 2019) and a greater understanding is required of current transmission trends.

Initial data from centres in London and Brighton suggests the incidence of acute hepatitis C has fallen significantly between 2015-8, likely as a consequence of more widespread access to treatment (Garvey et al., 2019). However, lack of access to treatment for reinfection means that incidence may begin to rise again.

With increasing access to pre-exposure prophylaxis (PREP), it is becoming clear that this population – almost entirely high-risk HIV negative MSM – have a high incidence of acute HCV with evidence of transmission between HIV positive and HIV negative groups.

#### 1.1.2.2 Acute HCV in People who inject drugs and other high-risk groups

PWID are thought to be the key risk group in driving the HCV epidemic in high income settings such as the UK, with over 60% of all those HCV positive reporting previous injecting drug use. As discussed above, PHE reporting in England focuses on proxy measures for acute infection in PWID as there is very little data on acute infection in this population. As part of measures to improve coverage of testing and treatment for HCV in PWID, there has been an expansion of programmes working in drug and alcohol support services (DAAS). Between 2009/10 and 2017/8 there have been significant improvement in testing those in drug and alcohol services (43% to 68%), adults newly presenting to services (37% to 53%) and in those who have ever injected (57% to 84%) with access to testing improving through use of dried blood spot (DBS) testing.

Another key focus for efforts towards eliminating hepatitis C transmission is individuals detained on remand or in prison, where injecting drug use is more prevalent than in the general population. Since the agreement (between PHE, NHS England and Her Majesty's Prison and Probation service, HMPPS) of opt-out testing for blood borne viruses in 2013 ,there has been a significant increase in testing (from 5.3% in 2010/1 to 19% in 2017/8) though still falling someway short of the NHSE target of 75%. More local services are extending into prisons for treatment and provide an opportunity to identify acute infection in these settings.

There are relatively few cases of acute HCV infection attributed to healthcare settings each, either in patients or healthcare providers.

### 1.1.3 Identification of Transmission Networks for HCV

Unlike other curable communicable diseases, contact tracing (the process of contacting individuals who may have either been the source of, or infected by the index individual) is not routinely practiced for HCV in the UK. As in some high-risk populations (particularly people living with HIV [PLWH]) and/or some centres managing HCV in the setting of an STI/HIV service contact tracing is performed using the existing partner notification tools for other sexually transmitted infections. Beyond these settings, there are little data on methods of contact tracing partners (sexual or injecting) and notification outcomes. This study will ascertain general methods used for contact tracing, the number of potential contacts per index case, the proportion that are contactable/uncontactable and the outcome of partner notification attempts.

### 1.1.4 Viral Sequencing and Insight into Transmission of HCV

Phylogenetic comparison of HCV genome sequences has provided further insights into the recent epidemic of HCV in HIV-infected MSM, with sequencing homology confirming common source transmission. Robust monophyletic transmission clusters have been identified within the MSM populations of urban centres in the UK, France, the Netherlands, Germany, Australia and Asia (van de Laar et al., 2007, Sun et al., 2012, Matthews et al., 2011, Danta et al., 2007, Serpaggi J, 2006, Vogel et al., 2010). An international collaborative study confirmed a large Europe-wide MSM-specific transmission network, which was separate from networks associated with non-MSM IDU transmission (van de Laar et al., 2009). Genetic divergence studies of these strains suggest multiple

independent introductions of HCV into the MSM community since the 1980s, most likely from the IDU population (van de Laar et al., 2007, Urbanus et al., 2009, Vogel et al., 2011).

### 1.1.5 Social Network Analysis

Phylogenetic techniques allow characterization of viral transmission events. Their use may be complemented by social network analyses, which describe interactions between individuals according to their social behavior and therefore characterise relationships likely to be associated with HCV transmission. Phylogenetic analyses have been combined with social network studies to identify possible intervention targets in the context of HIV transmission in Hong Kong MSM. Among 74 prospective recruits with primary HIV who were surveyed regarding venues used to source sexual partners, internet-centered and sauna-centered social clusters were identified, with partial overlap between phylogenetic and social clusters (Lee et al., 2009). Similarly, amongst a cohort of people who inject drugs in Melbourne, a strong correlation was found between the phylogeny and the injecting network (Sacks-Davis et al., 2012). In Australia, a strong correlation was identified between the sexual network of venues which HIV-positive MSM used to source sexual partners and the genetic relationships between infecting HCV strains (Bradshaw et al., 2013a).

## 1.2 RATIONALE FOR CURRENT STUDY

This study is part of a project that aims to contribute towards efforts to achieve elimination of HCV in the UK. We aim to do this by improving identification and treatment those at risk of passing on HCV, ready for a time when availability of treatment will not be the limiting factor in patients accessing care.

Firstly, we aim to establish a common approach to the identification and management of new and recent infections within NHS services by ensuring data is collected to identify networks of individuals where new infections are occurring. In particular, there are number of high-risk groups for HCV infection which are harder to engage in care and are important sources for new infections. This work will focus on these groups, such as those with HIV infection and those who are homeless or vulnerably housed. Detailed demographic, clinical and behavioral data will be captured to understand these groups in more detail.

Secondly, we aim to define networks of individuals transmitting HCV. By combining information on both individuals with recent hepatitis and more detailed information on their virus from new sequencing methods it will be possible to build a picture of how virus is being transmitted. Such data can be used to predict and test novel ways to tackle ongoing new infections and re-infections.

No study has examined the possible relationship between sexual networks involving both HIV-negative and HIV-positive MSM and the HCV phylogeny. Characterising the nature of these networks and their relationship to viral transmissions will allow optimization of public health interventions. Such interventions might include targeting of specific sex on premises venues, health promotion on mobile phone apps and internet websites used for sourcing sexual partners, and screening of high-risk HIV-negative and HIV-positive MSM.

Overall, we hypothesize that improved understanding and identification of acute HCV transmission events will aid progress towards achieving HCV elimination targets.

# 2. STUDY OBJECTIVES

Primary Objective:

- To identify and describe cases of acute Hepatitis C (HCV) infection in the United Kingdom

Secondary Objective(s):

- To describe risk factors for acute HCV that are amenable for prevention.
- To describe response to direct-acting antiviral treatment in the context of acute infection.
- To identify networks of ongoing transmission of HCV.
- To describe the rate of re-infection following successful treatment of acute HCV.
- To describe linkage to care and treatment in those with acute infection.
- To perform a phylogenetic analysis of HCV transmission within the UK.

Exploratory Objectives

- To describe the characteristics and magnitude of the HCV reservoir in peripheral blood mononuclear cells in patients with acute hepatitis C infection.
- To describe the host immune response to HCV in acute infection

# 3. STUDY DESIGN

The UKACH study is a prospective, observation, multi-centre cohort study of acute hepatitis C within the United Kingdom. We aim to enrol up to 300 participants over a period of three years. Individual participants will be followed up annually for three years from enrolment

## 3.1 Study outcome measures

Primary Outcome Measure(s)

- Descriptive statistics (n [%]) relating to participant characteristics (demographics and risk factors) and virus characteristics (genotype) at baseline and during follow up.

Secondary Outcome Measure(s)

- Descriptive statistics of risk factors collectively and by individual acquisition risk sub-groups, including but not limited to MSM, PWID, primary infection and re-infection. Analysis will be performed at baseline and at at timepoints 12, 24 and 36 months of follow-up.
- Proportion on patients with acute infection with an undetectable viral load at 3 years post enrolment; SVR at 12 weeks post completion of DAA treatment; SVR at 24 weeks post completion of DAA treatment; Treatment regimens and source (NHSE, clinical trial, self-sourced via internet); Analysis will be performed overall and by acquisition risk sub-group (including but not limited to MSM, PWID; primary infection and re-infection).
- Descriptive network analysis including clustering and geographic analysis based upon epidemiological data.

- Proportion of individuals meeting criteria for re-infection at month 12, 24 and 36 of follow up, collectively and by individual subgroup. Time to event analysis using Kaplan-Meir method from time since achieving sustained virological response.
- Proportion of cases under ongoing secondary care follow up defined as attending annual follow up visits in secondary care. Proportion of cases discharged from routine follow up owing to successful treatment; Proportion lost to follow up. Data summarised at timepoints 12, 24 and 36 months of follow-up.
- Phylogentic analysis using whole genome sequencing of HCV isolates; Maximum likelihood phylogenetic trees; Clustering analysis; Time to most recent common ancestor.

Exploratory outcome measures

- PCR and sequencing of HCV virus from sorted peripheral blood mononuclear cells.
- Exploratory immunological assays of HCV-specific humoral and cellular responses, including but not limited to ELISA, ELISPOT and flow cytometry.

## 3.2 Research Methods

- Participants will be identified on referral to an NHS outpatient clinic for investigation and management of Hepatitis C. Cases will be identified through their usual care team and referred to the research team. This may occur prior to attendance at the clinic or upon their first attendance.
- Eligibility checks (i.e. confirmation that the participant meets the criteria for acute Hepatitis C infection) will be confirmed by the research team in collaboration with the usual care team. This will involve access to medical and laboratory records, to review specific results including (but not limited to) previous testing of HCV and current liver function tests.
- Informed consent will be requested once eligibility has been confirmed. Potential participants will be provided with a study information booklet to review. They will be given time to consider the information contained therein and will be provided with access to a member of the study team to ask any questions. If they decide to participate, they will be asked to review, initial and sign an informed consent form. Participants will be provided with a copy of the consent form.
- Medical History. A focussed medical history will be conducted by a member of the research team after completion of informed consent. This will include as a minimum medical co-morbidity; previous HCV infection; previous HCV treatment; HIV co-infection and current medications. The medical history will be cross referenced with medical records. This will be recorded in the CRF.
- Review Laboratory Parameters. Baseline laboratory parameters (including serum alanine aminotransferase, bilirubin, albumin, urea & electrolytes/eGFR, coagulation screen, hepatitis C IgG, hepatitis C viral load) will be reviewed at baseline and recorded in the CRF.
- Questionnaire. Consenting participants will be provided with a study questionnaire. This comprises a series of questions that aims to understand what factors may have put a participant at risk for HCV infection and transmission. This will involve a series of detailed questions on your personal activities, including those such as drug use, sexual practices and medical procedures. All of this information will be collected in a strictly confidential and pseudonymised fashion. Participants will be identified only using a study identifier. Where location data is required, this will be identified using the first portion of the post-code only, minimising the risk of de-anonymisation.

Participants will be asked to complete the study questionnaire during their attendance at the clinic visit, where they will be given access to a member of the study team who can clarify any questions or areas of uncertainty. Upon completion, participants will hand the questionnaire to the study investigator, who will transcribe the data to a the eCRF. If participants do not wish to remain in the clinic, then will be allowed to take the questionnaire home and complete it in their own time. They will be asked to return the questionnaire to the study site and will be provided with instructions on how to return this.

- The study investigator will check if the participant has been referred for contact tracing by reviewing the medical notes and direct questioning of the participant.
- Blood sample. A blood sample will be collected at the first study visit. This will be collected either by a member of the research team or clinic phlebotomist. Blood samples will be couriered to the Molecular Diagnostics Unit at Imperial College London for further analysis.
- Continued consent will be collected at each subsequent clinic visit. This will be collated by a member of the study team.

# 4. PARTICIPANT ENTRY

## 4.1 Pre-registration evaluations

Participants will be approached for enrolment in the study if they are diagnosed with hepatitis C infection as part of routine clinical care. The decision to test for HCV will be at the discretion of the attending physician as clinically indicated. Active screening will not be performed, and enrolment will therefore be opportunistic. Active hepatitis C infection is typically diagnosed through the detection of anti-HCV IgG coupled with a positive HCV RNA, performed in an accredited laboratory.

Participants will be identified on referral to an NHS outpatient clinic for investigation and management of Hepatitis C. Cases will be identified through their usual care team and referred to the research team. This may occur prior to attendance at the clinic or upon their first attendance.

Eligibility checks (i.e. confirmation that the participant meets the criteria for acute Hepatitis C infection) will be confirmed by the research team in collaboration with the usual care team. This will involve access to medical and laboratory records, to review specific results including (but not limited to) previous testing of HCV and current liver function tests.

Informed consent will be requested once eligibility has been confirmed. Informed consent will take place at the NHS site where the outpatient clinic is situated. Potential participants will be provided with a study information booklet to review, either prior to attendance at the clinic or on first attendance. They will be given time (minimum of 24 hours) to consider the information contained therein and will be provided with access to a member of the study team to ask any questions. If they decide to participate, they will be asked to review, initial and sign an informed consent form. If they wish to take additional time to consider participation, they will be asked to provide contact details and to re-attend the clinic site at a later date to complete the informed consent form. Participants will be provided with a copy of the consent form.

After consent, the study investigators will perform a pre-enrolment check prior to formal enrolment. Study investigators will access laboratory records and health record to confirm that they meet the case definition for acute hepatitis C infection as defined in the inclusion and exclusion criteria.

## 4.2 Inclusion Criteria

All participants enrolled in the study will meet the following inclusion criteria

1. Aged ≥ 18 years
2. Willing to undergo at least one study visit at a study centre
3. To be able to give written, informed consent and undertake questionnaire in English
4. The patient must have evidence of acute hepatitis C infection defined according to established criteria as:
    a. a positive HCV RNA test in the presence of a negative anti-HCV test (HCV antibody and/or HCV antigen and/or HCV RNA) within the past 12 months;
    b. a positive HCV RNA test with an acute clinical hepatitis (clinically evident jaundice or alananine aminotransferase ≥ 5x the upper limit of normal reference range at the recruiting centre) with no other identifiable cause
    c. acute re-infection defined as a positive HCV RNA test in patients who had previously achieved spontaneous clearance (anti-HCV positive individuals with two consecutive negative HCV RNA results 24 weeks apart and did not receive treatment), sustained virologic response following treatment (negative HCV RNA result 24 (for IFN-based) or 12 weeks (DAA), after stopping treatment or later
    d. acute HCV re-infection as defined by evidence of HCV genotype switch

### 4.3 Exclusion Criteria

Participants will be excluded from participation in the study if the following criteria are met:

1. Evidence of HCV infection not consistent with the case definition for acute hepatitis C.

### 4.4 Withdrawal criteria

Participants may withdraw from all or any aspects of the study at any time and for any reason, without incurring any penalty or affecting their subsequent care. This is stated explicitly in the participant information sheet.

## 5. ADVERSE EVENTS

### 5.1 Definitions

**Adverse Event (AE):** any untoward medical occurrence in a patient or clinical study subject.

**Serious Adverse Event (SAE):** any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

### 5.3 Reporting Procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

#### 5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded.

#### 5.3.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death due to hepatitis C and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the London Westminster research ethics committee where in the opinion of the Chief Investigator, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

**Contact details for reporting SAEs**
**jrco@imperial.ac.uk**
**CI email (and contact details below)**
**Professor Graham Cooke**
**St Mary's Hospital,**
**Please send SAE forms to:**
**m.gibani@ic.ac.uk; g.cooke@ic.ac.uk**
**attention Dr Malick Gibani/Prof Graham Cooke**
**Tel: +44 (0)20 7594390 (Mon to Fri 09.00 – 17.00)**

## 6. ASSESSMENT AND FOLLOW-UP

### 6.1 Recruitment and retention strategies

Patients will be recruited from all services where they may attend for care. These will include, but not be limited to (i) acute medical services (ii) out-patient services (iii) primary care (iv) community outreach care, including those vulnerably housed and (v) drug and alcohol support services

In each setting, patients will be recruited through local clinical teams. Patients or participants will be identified on referral to an NHS outpatient clinic for investigation and management of Hepatitis C. Cases will be identified through their direct care team and referred to the study team with patient's permission. This may occur prior to attendance at the clinic or upon their first clinic attendance. The study team will then be approached the patients, provide them with participant information sheet and explain the study, the right not to take part or withdraw at any time and the overall purpose of

the study. Participants will be allowed at least 24 hours to decide on participation and will be encouraged to discuss their participation with relative and GP if they wish to do so.

### 6.2 Informed consent

The local PI or an appropriately trained member of the research team will seek written informed consent from patients to enter into the study. Individuals trained and responsible for taking consent will be documented on the trial's Delegation Log (with signatures). Consent will be sought after explanation of the aims, methods, benefits and potential hazards of the trial and BEFORE any trial-specific procedures are performed or any blood is taken for the study.

Consent will be taken by a member of the research team at the NHS site in the outpatient clinic or elsewhere at the study site. We will assess a participants' understanding of the purpose and nature of the research; what the research involves and the risks and benefits by providing them with a patient information sheet and a discussion with the patient/participant. The researcher will explain the study, the right not to take part or withdraw at any time and the overall purpose of the study. Participants will be allowed at least 24 hours to decide on participation and will be encouraged to discuss their participation with relative and GP if they wish to. Any questions that participants may have will be addressed and those participants who agreed to take part will be asked to sign a consent form. For those identified at clinic, participants will then be asked to complete the study questionnaire which could be completed either at the clinic or at home.

The individual taking consent must make it clear that the participant is free to refuse to participate in or withdraw from all or any aspects of the study at any time and for any reason, without incurring any penalty or affecting their subsequent care. This is stated explicitly in the participant information sheet.

Signed consent forms must be kept by the investigator and documented in the case record form (CRF) and a copy given to the participant. The participant will be allowed at least 24 hours to consider the information, and the opportunity to ask questions to decide whether they will participate in the study.

A patient may consent to only provide answers to questionnaire and not consent to a blood sample; in which case they can still be enrolled in the study.

### 6.3 Enrolment

Patients are anonymized by assigning to each of them a unique study code. The list of codes will be kept by each single participating investigator. Duplicate enrolments are ruled out by identifying each participant (apart from the study code) with his/her date of birth, sex and height.

Participants will not be provided with any payment or any sort of compensation for medical and other costs incurred during the time of participation to the study. Patients undergo all routine examinations including clinical consultations, blood tests, ultrasound examination of the abdomen, liver biopsy, non-invasive assessments of liver fibrosis – as required by the usual diagnostic and therapeutic management of patients with HCV infection according to the state-of-the-art knowledge in the field: thus, the cost of these medical procedures are not covered by the study. No additional interventions – diagnostic or therapeutic – are required in association with the participation with the study. Patients are requested only to allow the collection of their blood in the total amount of ~20 ml once a year, but the material and the procedures associated with this are entirely free of charge.

Given the observational nature of the study, participants will be able to enrol in other studies (e.g. a treatment study for acute hepatitis C infection) in line with the criteria stipulated in those studies.

## 6.4 Study Assessment Schedule

Participants will be followed up at annual assessments at months 12, 24 and 36 from enrolment. A window period of +/- 56 days will apply for each follow up visit. It is acknowledged that the population at study may have difficulty attending follow up visits at defined intervals – therefore, in exceptional circumstances, participants may attend follow up visits outside of the defined window period (i.e. +/- 56 days) at the discretion of the principal investigator at each site and a written justification should be provided in the participants case record file.

***Visit 0***

The first visit will be used to assess eligibility and obtain informed consent. This visit is considered as Day 0. The baseline data collection is estimated to take ~1 hour.

All eligible and consenting participants will be asked to

- give permission for demographic and clinical data to be collected
- provide additional information via questionnaire related to risks for infection
- provide a single blood draw (20mls) to allow genotypic analysis of the HCV virus with which they are infected.

***Visit 1 (Month 12 +/- 56 Days); Visit 2 (Month 24 +/- 56 Days) and Visit 3 (Month 36 +/- 56 days)***

Follow up data will be collected at annual intervals from enrolment (+/- 56 days as outlined above). The follow up data collection is estimated to take ~1 hour.

All eligible and consenting participants will be asked to

- give ongoing consent for participation in the study.
- Give permission for collection of updated demographic and clinical data to be collected.
- provide updated acquisition risk factors additional information via questionnaire related to risks for infection.
- If there is evidence of re-infection provide a single blood draw (20mls) to allow genotypic analysis of the HCV virus with which they are infected.

Study investigators will collect information relating to:

- Spontaneous clearance
- Initiation of treatment
- Treatment regimen (if treatment initiated)
- Response to treatment (SVR at 12 weeks; SVR at 24 weeks)
- Evidence of re-infection.
- Engagement with contact tracing.

## 6.5 Follow up study visits

Data will be captured from routine records and a short behavioural questionnaire to assess ongoing risk for transmission/reinfection.

### 6.6 Behavioral data

All participants will be asked to identify potential risks of transmission including medical and cosmetic procedures, use of recreational drugs and sexual behaviour. Information will be collected on potential exposure within the last year.

For medical procedures this will include (i) nature of procedure (ii) location of procedure (iii) date of procedure, including tattoos and piercings.

For recreational drug use with will include (i) type of drug(s) used (ii) frequency of drug use (iii) route of drug administration (iv) sharing of needles or other paraphernalia (v) venue(s) for drug use.

For sexual behaviour (i) nature of sexual contact (ii) frequency of sexual contact (iii) engagement in high risk behaviour e.g. group sex, fisting, testing and treatment for sexually transmitted infections.

### 6.7 Analysis of viral transmission, viral reservoirs and HCV specific immune responses

Current management of HCV-infected individuals requires viral genotyping to determine the choice and duration of therapy. Methods used vary between laboratories. Public Health England have recently switched to next generation sequencing (NGS)/whole genome sequencing (WGS) for genotyping and detection of resistance associated substitution (RAS) testing. Whole viral sequence is able to provide the genotyping and resistance data required for clinical decision making, but also richer information on which transmission dynamics may be explored. After transmission, HCV rapidly multiplies in a new host into large numbers of genetically distinct but similar variants (quasispecies). Standard Sanger sequencing methods only detect majority sequences; whereas detection of minority variants by “deep” (NGS) sequencing can both improve sensitivity (Montoya et al., 2016) and also provide the rich data on which linked transmissions can be identified.

In this study, we will evaluate different methods for NGS HCV sequencing (Thomson et al., 2016) and evaluate the applicability of NGS HCV sequencing in clinical services. Viral sequence will be used to identify potential transmissions between infected individuals and help to define transmission networks. If patients give appropriate consent at baseline, a 20ml blood draw will be taken in an EDTA tube (2 x 10ml EDTA tubes). We will collect additional samples at follow up timepoints, if there is clinical evidence of HCV re-infection following successful treatment. Samples should be refrigerated at 4° until shipped to central laboratories at the Molecular Diagnostics Unit (MDU) at Imperial College. Participating sites will be provided with courier instructions.

Although the hepatitis C virus primarily infects hepatocytes, several studies have described replication and establishment of a reservoir within peripheral blood mononuclear cells (PBMCs)(Ito et al., 2011). Infection of host immune cells may be associated with extra-hepatic manifestations of HCV infection(Kondo & Shimosegawa, 2013). In is unclear whether peripheral blood reservoirs are established early in acute infection and whether the establishment of a peripheral reservoir is related to an ineffective host immune response in early infection (Shin et al., 2016). To that end, we will use the same blood sample to perform an analysis of the characteristics and magnitude of HCV reservoirs in peripheral blood mononuclear cells, as well as analysing HCV specific immune responses in acute infection.

### 6.8 Blood Sampling and Laboratory Analysis

Additional blood samples will be collected for viral analysis as detailed above. The samples will be collected, stored, and pseudonymised at enrolment. Samples will be collected according to standard local procedures. Samples will be transferred to Imperial College periodically as determined by the study team.

### 6.9 Loss to Follow-up and transfer of care

In the statistical analysis, a participant will be classified as 'lost to follow-up' if they have not attended their final follow-up visit (i.e. 36 months +/- 56 days). A patient will be deemed to have transferred care if no longer attend the service from which they were enrolled but attend at least two visits at an alternative care setting. Should a patient choose to transfer to another centre, it would be possible to reenrol them in the study at an alternative site.

### 6.10 Study Withdrawal

In consenting to the study, participants are consenting to collection of their data, both directly from them and their clinical records.
Participants may be considered withdrawn from the study if:

- The participant chooses to withdraw informed consent
- The participant dies
- The participant prefers not to attend the relevant study site.

### 6.11 End of Study

The study end will be defined as when the final participant attends their final follow up visit or is lost to follow up.

## 7. STATISTICS AND DATA ANALYSIS

### 7.1 Sample size

No formal sample size calculations have been made for this observational study. In total we aim to enrol 300 participants. This number largely reflects a convenience sample given the duration and budget of the study and has been chosen in light of previous studies – in one study conducted between 2013 to 2018, 293 case of acute HCV were identified across three central London hospitals. Whilst overall rates of new acute HCV infections appear to be falling, rates of re-infection appear to be increasing. We plan to enrol cases across a wider number of sites within London as well as conducting an enhanced surveillance. We estimate that case accrual can continue until 300 participants are recruited – case accrual rates will be reviewed on a 3-monthly basis. The study will run for three years from initiation, defined as recruitment of the first participant.

### 7.2 Statistical Analysis Plan

The majority of analysis in the study will be descriptive in nature, comprise counts and percentages.

The analyses for the primary endpoint will be descriptive in nature and will not include formal hypothesis testing.

Where appropriate, time-to-event endpoints analyses will be conducted using the Kaplan-Meier method and presented as Kaplan-Meier plots.

### 7.3 Sub-group analysis

We will perform an analysis of primary and secondary analysis on distinct sub-groups as defined below:

- HIV-HCV co-infection;
- Men who have sex with men (MSM);
- People who inject drugs (all, active injection drug users, previous injection drug users);
- Acute primary HCV infection;
- Acute HCV re-infection following previous successful treatment

### 7.4 Source data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, and correspondence. CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

### 7.5 Direct Access to Participant Records

Participating investigators should agree to allow study related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents if required. Participants' consent for this must be obtained. Such information will be treated as strictly confidential and will in no circumstances be made publicly available.

The following data should be verifiable from source documents:

- all signed consent forms
- dates of assessments including dates specimens were taken and processed in the laboratory
- eligibility and baseline values for all participants
- routine participant clinical and laboratory data.

### 7.6 Data collection and management responsibilities

Study data will be collected by study investigators included in the delegation log.

Data collection and storage will be inspected throughout the study by internal and external (by the study Sponsor) monitoring.

Direct access will be granted to authorised representatives from the Sponsor and host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. The sponsor will have access to raw, pseudonymised data on reasonable request.

### 7.7 Data Recording and Record Keeping

The study team will populate the content of participants' CRFs, which will be in a paper and/or electronic format, using REDCap™ database. This database is stored on a secure server within the UK at Imperial College London and has restricted access and is password-protected with accountability records. This data includes safety data, laboratory data (both clinical and immunological) and outcome data. All information transcribed to and from the RedCap™ database is by encrypted (Https) transfer.

Each study participant will have a participant number allocated at the time of enrolment. After enrolment, participants will be identified by a study specific participant number and/or code. Samples sent to laboratories for processing will be identified by, participant number, randomised laboratory number and participant initials.

Pseudonymised CRFs and any other documents related to primary and secondary endpoints of the study will also be transmitted to the Sponsor at completion of the study. This will be held at Imperial College archives and Corporate Records Units (ACRU). Pseudonymised CRFs and any other documents related to primary and secondary endpoints of the study will also be transmitted to the Sponsor at completion of the study.

## 8. REGULATORY ISSUES

### 8.1 Ethics approval

The Study Coordination Centre has obtained approval from the London Westminster Research Ethics Committee (REC) and Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

### 8.2 Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered, and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

### 8.3 Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the fulfil transparency requirements under the General Data Protection Regulation for health and care research.

### 8.4 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

### 8.5 Sponsor
Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

### 8.6 Funding
The trial is supported by an award from the National Institute of Healthcare Research (NIHR, UK)

### 8.7 Audits
The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research.

## 9. STUDY MANAGEMENT

A Study Management Group (SMG) will be formed to conduct the day-to-day management of the study. This will include the Chief Investigator, Site PI, Trial Statistician, Clinical Project Manager, Trial Manager, Lab Manager and Data Manager. The group will meet at least once per month, although may meet more or less often as required. The group will discuss issues related to the progress of the trial at the site and to ensure that the trial is running well.

The full details can be found in the SMG Charter.

## 10. PUBLICATION POLICY

The Chief Investigator will co-ordinate dissemination of data from this study. All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study will be reviewed by any site sub-investigator and by the Sponsor prior to submission. All communication or publications concerning the project, including at a conference or seminar, shall acknowledge the financial contribution of the NIHR.

## 10. REFERENCES

Boerekamps, A., Newsum, A. M., Smit, C., Arends, J. E., Richter, C., Reiss, P., Rijnders, B. J. A., Brinkman, K., van der Valk, M., Geerlings, S. E., Godfried, M. H., Goorhuis, A., Hovius, J. W., van der Meer, J. T. M., Kuijpers, T. W., Nellen, F. J. B., van der Poll, D. T., Prins, J. M., van Vugt, H. J. M., … Tuk, B. (2018). High Treatment Uptake in Human Immunodeficiency Virus/Hepatitis C Virus–Coinfected Patients After Unrestricted Access to Direct-Acting Antivirals in the Netherlands. *Clinical Infectious Diseases*, *66*(9), 1352–1359. https://doi.org/10.1093/cid/cix1004

Boerekamps, A., van den Berk, G. E., Lauw, F. N., Leyten, E. M., van Kasteren, M. E., van Eeden, A., Posthouwer, D., Claassen, M. A., Dofferhoff, A. S., Verhagen, D. W. M., Bierman, W. F., Lettinga, K. D., Kroon, F. P., Delsing, C. E., Groeneveld, P. H., Soetekouw, R., Peters, E. J., Hullegie, S. J., Popping, S., … Rijnders, B. J. (2018). Declining Hepatitis C Virus (HCV) Incidence in Dutch Human Immunodeficiency Virus-Positive Men Who Have Sex With Men After Unrestricted Access to HCV Therapy. *Clinical Infectious Diseases*, *66*(9), 1360–1365. https://doi.org/10.1093/cid/cix1007

Cooke, G. S., Andrieux-Meyer, I., Applegate, T. L., Atun, R., Burry, J. R., Cheinquer, H., Dusheiko, G., Feld, J. J., Gore, C., Griswold, M. G., Hamid, S., Hellard, M. E., Hou, J. L., Howell, J., Jia, J., Kravchenko, N., Lazarus, J. V., Lemoine, M., Lesi, O. A., … Yau, J. (2019). Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission. In *The Lancet Gastroenterology and Hepatology*. https://doi.org/10.1016/S2468-1253(18)30270-X

Garvey, L., Smith, C. J., Stingone, C., Ghosh, I., Rodger, A., Jain, L., Sood, C., Mahungu, T., Freeman, C., Dakshina, S., Ferro, F., Waters, L., Brown, A., Cooke, G., & Bhagani, S. (2019). *FALL IN HCV INCIDENCE IN HIV+ MSM IN LONDON FOLLOWING WIDER ACCESS TO DAA THERAPY | CROI Conference*. http://www.croiconference.org/sessions/fall-hcv-incidence-hiv-msm-london-following-wider-access-daa-therapy

Heffernan, A., Cooke, G. S., Nayagam, S., Thursz, M., & Hallett, T. B. (2019a). Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model. *The Lancet*. https://doi.org/10.1016/S0140-6736(18)32277-3

Heffernan, A., Cooke, G. S., Nayagam, S., Thursz, M., & Hallett, T. B. (2019b). Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model. *The Lancet*, *393*(10178), 1319–1329. https://doi.org/10.1016/S0140-6736(18)32277-3

Ito, M., Kusunoki, H., & Mizuochi, T. (2011). Peripheral B cells as reservoirs for persistent HCV infection. *Frontiers in Microbiology*. https://doi.org/10.3389/fmicb.2011.00177

Kondo, Y., & Shimosegawa, T. (2013). Direct effects of hepatitis C virus on the lymphoid cells. *World Journal of Gastroenterology*. https://doi.org/10.3748/wjg.v19.i44.7889

Lazarus, J. V., Wiktor, S., Colombo, M., & Thursz, M. (2017). Micro-elimination – A path to global elimination of hepatitis C. In *Journal of Hepatology*. https://doi.org/10.1016/j.jhep.2017.06.033

Martin, N. K., Hickman, M., Hutchinson, S. J., Goldberg, D. J., & Vickerman, P. (2013). Combination interventions to prevent HCV transmission among people who inject drugs: Modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy. *Clinical Infectious Diseases*. https://doi.org/10.1093/cid/cit296

Martin, N. K., Thornton, A., Hickman, M., Sabin, C., Nelson, M., Cooke, G. S., Martin, T. C. S., Delpech, V., Ruf, M., Price, H., Azad, Y., Thomson, E. C., & Vickerman, P. (2016). Can Hepatitis C Virus (HCV) Direct-Acting Antiviral Treatment as Prevention Reverse the HCV Epidemic among Men Who Have Sex with Men in the United Kingdom? Epidemiological and Modeling Insights. *Clinical Infectious Diseases*. https://doi.org/10.1093/cid/ciw075

Mcauley, A., Palmateer, N., Goldberg, D., Shepherd, S., Gunson, R., & Hutchinson, S. (2019). *The Needle Exchange Surveillance Initiative (NESI): Prevalence of blood-borne viruses and injecting risk behaviours among people who inject drugs (PWID) attending injecting equipment provision (IEP) services in Scotland, 2008-09 to 2017-18.*

Montoya, V., Olmstead, A., Tang, P., Cook, D., Janjua, N., Grebely, J., Jacka, B., Poon, A. F. Y., & Krajden, M. (2016). Deep sequencing increases hepatitis C virus phylogenetic cluster detection compared to Sanger sequencing. *Infection, Genetics and Evolution*, *43*, 329–337. https://doi.org/10.1016/J.MEEGID.2016.06.015

PHE. (2018). *Hepatitis C treatment monitoring in England: Content, completeness and preliminary findings from the Hepatitis C patient registry and treatment outcome system*. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/756748/HCV_treatment_monitoring_report_2018.pdf

PHE. (2019). *Hepatitis C in England 2019: Working to eliminate hepatitis C as a major public health threat*. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/798270/HCV_in-England_2019.pdf

Popping, S., Hullegie, S. J., Boerekamps, A., Rijnders, B. J. A., de Knegt, R. J., Rockstroh, J. K., Verbon, A., Boucher, C. A. B., Nichols, B. E., & van de Vijver, D. A. M. C. (2019). Early treatment of acute hepatitis C infection is cost-effective in HIV-infected men-who-have-sex-with-men. *PLOS ONE*, *14*(1), e0210179. https://doi.org/10.1371/journal.pone.0210179

Pradat, P., Huleux, T., Raffi, F., Delobel, P., Valantin, M.-A., Poizot-Martin, I., Pugliese, P., Reynes, J., Rey, D., Hoen, B., Cabie, A., Bani-Sadr, F., Cheret, A., Duvivier, C., Jacomet, C., Fresard, A., Hustache-Mathieu, L., Cotte, L., & Dat'AIDS study Group. (2018). Incidence of new hepatitis C virus infection is still increasing in French MSM living with HIV. *AIDS*, *32*(8), 1. https://doi.org/10.1097/QAD.0000000000001789

Shin, E. C., Sung, P. S., & Park, S. H. (2016). Immune responses and immunopathology in acute and chronic viral hepatitis. In *Nature Reviews Immunology*. https://doi.org/10.1038/nri.2016.69

Sikavi, C., Chen, P. H., Lee, A. D., Saab, E. G., Choi, G., & Saab, S. (2018). Hepatitis C and human immunodeficiency virus coinfection in the era of direct-acting antiviral agents: No longer a difficult-to-treat population. *Hepatology*. https://doi.org/10.1002/hep.29642

Stanaway, J. D., Flaxman, A. D., Naghavi, M., Fitzmaurice, C., Vos, T., Abubakar, I., Abu-Raddad, L. J., Assadi, R., Bhala, N., Cowie, B., Forouzanfour, M. H., Groeger, J., Hanafiah, K. M., Jacobsen, K. H., James, S. L., MacLachlan, J., Malekzadeh, R., Martin, N. K., Mokdad, A. A., … Cooke, G. S. (2016). The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. *The Lancet*. https://doi.org/10.1016/S0140-6736(16)30579-7

Sulkowski, M. S. (2019). The Proof Is in the Patient: Hepatitis C Virus Microelimination in the Swiss Human Immunodeficiency Virus Cohort Study. *Clinical Infectious Diseases*, *68*(4), 577–579. https://doi.org/10.1093/cid/ciy551

Thomson, E., Ip, C. L. C., Badhan, A., Christiansen, M. T., Adamson, W., Ansari, M. A., Bibby, D., Breuer, J., Brown, A., Bowden, R., Bryant, J., Bonsall, D., Da Silva Filipe, A., Hinds, C., Hudson, E., Klenerman, P., Lythgow, K., Mbisa, J. L., McLauchlan, J., … Simmonds, P. (2016). Comparison of Next-Generation Sequencing Technologies for Comprehensive Assessment of Full-Length Hepatitis C Viral Genomes. *Journal of Clinical Microbiology*, *54*(10), 2470–2484. https://doi.org/10.1128/JCM.00330-16

Trickey, A., Fraser, H., Lim, A. G., Peacock, A., Colledge, S., Walker, J. G., Leung, J., Grebely, J., Larney, S., Martin, N. K., Hickman, M., Degenhardt, L., May, M. T., & Vickerman, P. (2019). The contribution of injection drug use to hepatitis C virus transmission globally, regionally, and at country level: a modelling study. *The Lancet. Gastroenterology & Hepatology*, *4*(6), 435–444. https://doi.org/10.1016/S2468-1253(19)30085-8