ISRCTN72038467

Final Report

Evaluating the **P**opulation **I**mpact of Hepatitis C Direct Acting Antiviral **T**reatment as Prevention f**o**r **Pe**ople Who Inject Drugs (EPIToPe)

Authors:

Hickman M[1,3], Hutchinson S[3,7], Dillon JF[2], Vojt G[3], De Angelis D[4], Vickerman P[1], Family H[1], Mandal S[8] (Work-stream Leads/co-Leads)

Co-I and Research contributors:- Barnsdale, L[7], Beer LJ[2], Biggam C[3], Byrne, CJ[2,6,7], Desai, M[8], Donnan PT[2], Drysdale K[5], Elliott, L[3] Eriksen A[6], Flowers P[3], Foster G[5], Fraser H[1], Goldberg D[7,3], Hollingworth W[1], Glass R[8], Graham L[7], Gunson R[11], Hamilton E[9], Harris H[8], Harris M[12], Harris R[8], Heinsbroek E[8], Hope V[13], Horwood J[1], Horsburgh, K[9], Ijaz S[8], Inglis SK[2], Innes H[3], Johnson D[1], Jones H[1], Kipkoech K[1], Kundu B[1], Lane A[1], Liddell D[9], MacLeod K[9], Markoulidakis A[1,7], Martin NK[10,1], McAuley A[3,7], McCormick D[7], McCulloch P[1], McDonald S[3], Meadows J[1], Metcalfe C[1], Migchelsen S[8], Mitchell H[8], Murray A[9], Myring G[1], Palmateer N[3], Presanis A[4], Radley A[6], Ramsay M[8], Samartsidis P[4], Simmons R[8], Sinka K[8], Smith S[3], Stephens B[6], Thain D[6], Thorne B[1], Trayner K[3], Ward Z[1], Whiteley D[3], Wallace J[9], Yeung A[3]

Affiliations

1 Population Health Sciences, Bristol Medical School, University of Bristol

2 University of Dundee

3 School of Health and Life Sciences, Glasgow Caledonian University

4 MRC Biostatistics Unit, University of Cambridge

5 Barts Liver Centre, Queen Mary University of London

6 NHS Tayside Health Board

7 Public Health Scotland

8 UK Health Security Agency (UKHSA)

9 Scottish Drug Forum

10 Division of Infectious Diseases and Global Public Health, University of California San Diego

11 West of Scotland Specialist Virology Centre, Glasgow Royal Infirmary

12 London School of Hygiene and Tropical Medicine

13 Liverpool John Moores University

ABSTRACT

Introduction:

Model evidence suggested that Hepatitis C Virus (HCV) treatment scale-up could reduce HCV prevalence and incidence among People who inject drugs (PWID). We aimed to generate empirical evidence on this HCV "Treatment as Prevention" (TasP) hypothesis.

Methods:

Mixed methods study, including qualitative, statistical, mathematical and economic evaluation, of a natural experiment of HCV TasP in UK.

Findings

We demonstrated that rapid large-scale increase in HCV treatment in PWID could be successfully delivered in community settings, with Tayside exceeding local and WHO HCV care cascade targets for proportion of people with HCV diagnosed and treated.

We enhanced HCV surveillance with Public Health Scotland to create new linked datasets: Substance Use and Health Intelligence Linked Dataset (SHIeLD) and developed novel methods - Multiple Parameter Estimation of Prevalence (MPEP) – using SHIeLD to estimate prevalence of people dependent on opioids used in our HCV models.

We interviewed 40 service providers including peer workers, and 31 service users across the different community pathways in Tayside and co-produced a manual on how to scale-up treatment across the UK.

We developed a statistical model for evaluating HCV TasP based on biobehavioural survey data of PWID in England and Scotland which generated trends in chronic HCV and the counterfactual (chronic HCV in absence of community scale-up of HCV treatment based on pre-intervention trends).

We showed Scotland and England are likely to meet WHO elimination targets by 2030 and that community scale-up of HCV testing and treatment was highly cost-effective and might be cost-saving.

Qualitative interviews in 2023-24 with community teams in England found that normalising testing and treatment and peer support contributed to the success of the scale up.

Implications

Scaling-up HCV testing and treatment in the community and TasP is not only possible but highly effective – improving population health, reducing infections and saving NHS resources.

Plain English Summary

Hepatitis C virus can cause serious liver disease. People who have injected drugs are the main group of people in the UK living with Hepatitis C and at risk of getting new infections. The EPIToPe research programme followed the rapid scale up of hepatitis c testing and treatment in England and Scotland.

What we found:

- Our pilot in Tayside, Scotland, showed that rapid scale up of testing and treatment was possible.
- We developed recommendations for scale up in other areas, and showed that this pilot achieved World Health Organization hepatitis C targets for eliminating hepatitis c as a public health problem.
- We showed that treatment as prevention worked – the more that testing and treatment was scaled up – the bigger the impact was on reducing the number of people who were found to have hepatitis c virus amongst people who inject drugs.
- We enhanced national data sets and developed new methods to measure the number of people who inject drugs and trends in hepatitis c virus.
- New models for Scotland and England showed that both were on track to reduce new hepatitis c infections among people who inject drugs to below 2% per year before 2030.
- We showed that scaling up hepatitis c treatment and testing was highly cost-effective through preventing future severe liver disease and new infections. It also may be cost-saving, depending on how big the discount negotiated by government in the cost HCV drugs is.
- In England, two key features of the successful scaling up of HCV testing and treatment were peer workers acting as role models and supporting people through testing and treatment and local services “normalizing” testing and treatment.

Why this matters:
Testing and treating hepatitis C in the community is possible and highly effective - improving health, reducing infections and saving NHS resources.

Ethics and Dissemination

Extending HCV community care pathways is covered by ethics (ERADICATE C, ISRCTN27564683, Super DOT C Trial clinicaltrials.gov:NCT02706223). Ethical approval for extra data collection from patients including health utilities and qualitative interviews has been granted (East of Scotland Research Ethics Service REC 1 (ref: 18/ES/0128). ISCRCTN registration 72038467). University of Bristol Faculty of Health Research Ethics Committee approval (Ref: 14892, 07/06/2023) and Health Research Authority (HRA) governance approval (IRAS: 330743, 10/08/2023) was obtained for interviews with service providers and operational delivery networks in England. There have been multiple conference and expert and policy meetings presentations throughout the EPIToPe programme. In 2025-26, key EPIToPe findings will be presented to clinical and policymakers meetings in Scotland and England and at specific sessions held at UK Study of Society of Addiction (SSA) and International Conference on Health and Hepatitis in Substance Users (INHSU).

Strengths and limitations of this study

1. Intensity of HCV treatment scale-up could not be randomised making inference and estimation of intervention effect more uncertain.
2. Sero-behavioural surveillance has low power in some regions of UK.
3. There is a unique wealth of public health surveillance data in UK – compared to many other countries – which when combined with adaptable and extendable statistical and mathematical models, that incorporate additional evidence, can generate valid estimates of counterfactual (no community treatment scale-up) and HCV TasP intervention effect. These models can track and project progress towards meeting WHO targets to eliminate HCV as a public health problem.

Introduction and Background:

Infection with Hepatitis C Virus (HCV) is a progressive disease that over 20-40 years can lead to liver cancer and premature death. HCV is the second largest contributor to liver disease in the UK and one of the few causes that is curable[1]. New Direct Acting Antiviral (DAA) HCV drugs cure over 90% of patients within 8-12 weeks with few side-effects. This led World Health Organization (WHO) to develop strategies to eliminate HCV as a public health problem [2]. Key targets for HCV elimination in People Who Inject Drugs (PWID), adopted by UK, is to reduce HCV incidence to an absolute target of <2 per 100 person years (previously expressed as an 80% reduction in HCV transmission) [3].

Price reductions negotiated by NHS England (and other UK governments) combined with removal of previous restrictions/recommendations to prioritise treatment to people with severe liver disease afforded opportunity to substantially scale-up HCV treatment. Prior to HCV treatment scale-up it was estimated that approximately 150-200,000 people were infected with HCV in the UK, over 85% of whom are people who inject or have injected drugs[4-7] and chronic HCV prevalence and incidence among PWID varied from 20-50% and 5 to 15 per 100 person- years respectively[6 8-18]. Primary prevention, including opioid agonist treatment (OAT) and needle and syringe programmes (NSPs), are effective and can reduce the risk of HCV transmission by 50-80% [19-22]. However, HCV transmission models suggest that primary prevention through NSP and OST alone is insufficient to achieve substantial reductions (of the order of 40% or more within ten years) in HCV prevalence among PWID in the UK[23 24].

Instead model evidence supported the hypothesis that HCV Treatment scale-up for PWID (aka HCV Treatment as Prevention) could enhance other primary interventions and reduce HCV incidence and chronic prevalence to negligible levels (i.e. towards elimination as a major public health concern)[25-30]. Cost-effectiveness models also suggest early treatment should be prioritised to PWID over other patient groups (unless chronic HCV prevalence and transmission is very high)[31]. However, historically HCV treatment rates in PWID were too low to detect changes in HCV incidence and prevalence[9 32].

In a pilot study ("Eradicate C") in Tayside we showed that we can increase HCV case-finding and engage and successfully treat PWID in the community[33,34]. Our programme aimed to generate UK empirical evidence on the effectiveness of HCV 'Treatment as Prevention' (TasP) in people who inject drugs (PWID)[35].

Methods:

We conducted a mixed methods study, including qualitative studies and statistical, mathematical and economic evaluation, of a natural experiment of HCV TasP among PWID. We also developed methods for evaluating HCV TasP and monitoring progress towards HCV elimination targets.

Overview and summary findings

Our Programme has 5 work streams

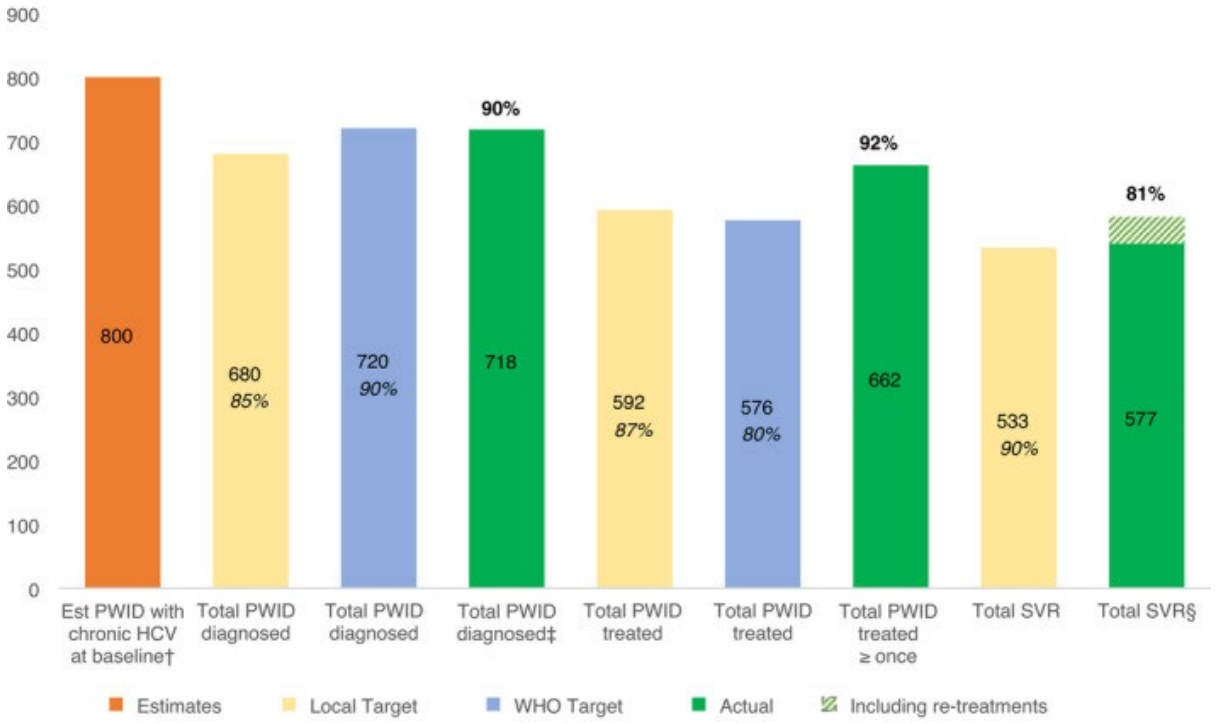
Workstream 1 (WS1) HCV Treatment Scale-up in Tayside

Tayside was our first intervention site as an early adopter of HCV treatment in the community, developing multiple novel HCV care pathways, and through combining support from Scottish Government, National Health Board Tayside (NHS Tayside) and industry (MSD, Gilead, BMS) could deliver rapid intensive scale-up of HCV treatments for PWID. The intervention was an intensive scale-

up of HCV treatment through the expansion of community HCV care pathways. No new clinical procedures or treatments were investigated and all PWID with chronic HCV were offered oral DAA HCV treatment in line with Scottish and UK clinical guidelines and provided free of charge to NHS patients [36]. Community HCV specialist nurses (3.5 FTE) coordinated and delivered case-finding and treatment across the pathways in Tayside – which are further investigated in WS3. Preliminary modelling – set out in our protocol – hypothesised that if an extra 500 PWID were treated over a short period (originally 2 years, though interrupted by COVID-19) then chronic HCV prevalence among PWID would reduce by approximately 62% from 26% (95% CrI 20-32) to at least 10% and chronic HCV incidence would fall from 4.2 (95% CrI 2.4-7.1) per 100 person-years (p100py) to 1.4 (95%CrI 1.0 – 1.4) p100py [35].

The rapid large-scale increase in HCV treatment was successfully delivered (see Cascade of Care Figure 1)[37]. Tayside exceeded local and WHO targets for HCV treatment care cascade – diagnosing approximately 90% of cases and treating over 80%. Decentralised care pathways in harm reduction, other drug services and prisons were critical as described in [37-39] with only 13% of HCV treatments delivered in hospital and remainer in the community. Updated evidence (WS4&5) below shows that Tayside has met WHO targets – reducing HCV incidence to below 2 per 100 person years and reducing chronic HCV by > 80%.

FIGURE 1 Tayside HCV Treatment Scale-up Cascade of Care[37].



From Aliment Pharmacol Ther 2021 Dec 8;55(5):568–579. doi: 10.1111/apt.16728. Estimated HCV Care Cascade in Tayside population of People Who Inject Drugs, alongside targets and outcomes for HCV diagnosis and treatment in the scaleup period. Est, estimated; HCV, hepatitis c virus; PWID, people who inject drugs; SVR, sustained virologic response; WHO, World Health Organization. Note: percentages rounded to the nearest whole number. Intention-to-treat and per-protocol rates were reported for SVR. †Based on 29% estimated chronic infection in a population of 2,800 people who inject drugs. ‡Total with ≥one HCV RNA positive test from June 2016 to April 2020 on the national clinical database. 2016 diagnoses included as they will have been eligible

for treatment at beginning of treatment scaleup in 2017. §Proportion of all treated cases (not treated individuals). SVR was 91% in cases with a documented test

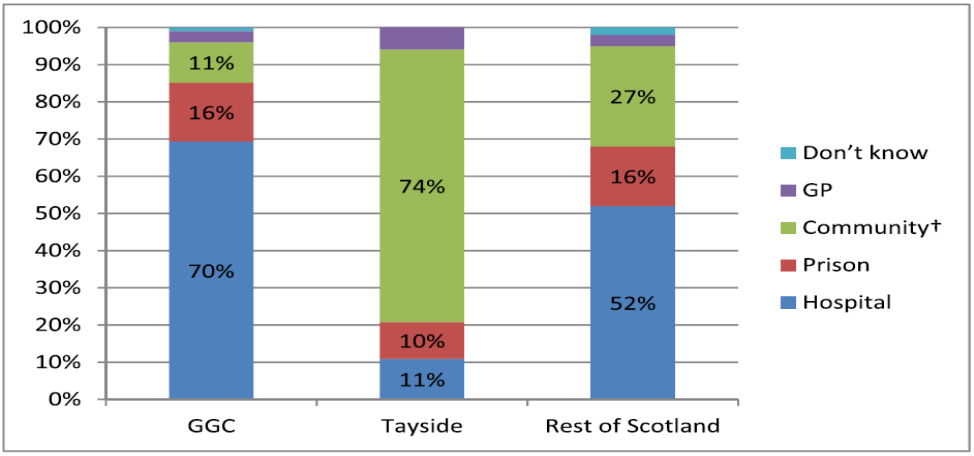
WS 2 – Enhancing HCV surveillance and epidemiology in PWID

The UK is one of few countries worldwide to have an established nationwide surveillance system monitoring HCV infection among PWID through a series of cross-sectional voluntary anonymous surveys of PWID recruited at harm reduction services, referred to as the Unlinked Anonymous Monitoring Programme (UAM) in England and Wales and the Needle Exchange Surveillance Initiative (NESI) in Scotland[40 41]. In addition, the UK has established sentinel laboratory surveillance of HCV testing and national monitoring of HCV treatment [10 42-44].

WS2.1 Enhancing Public Health Surveillance to Measure Chronic HCV in PWID

EPIToPe funded the 2019/20 wave of NESI including recruitment in Tayside (327), Glasgow (1072) and rest of Scotland (1101) achieved ahead of schedule, prior to suspension of recruitment in March 2020 due to COVID. [Needle Exchange Surveillance Initiative (NESI)]. EPIToPe funded HCV PCR testing of approximately 14,800 UAM stored samples for 2011-2018 [People who inject drugs: HIV and viral hepatitis monitoring - GOV.UK] and retrospective PCR testing of ~2400 NESI samples from 2011/12 and 2013/14. Prospectively both UAM and NESI test for HCV PCR and antibody. These real-world data were central to analyses showing increases in HCV treatment in the community and trends in chronic HCV in PWID (WS4) [38 45 46]. For example, see Figure 2 which shows that in 2017-18 the majority of HCV treatments in Tayside occurred in the community whereas 70% and over half of HCV treatments occurred in hospital in Glasgow and rest of Scotland and Glasgow respectively[38].

Figure 2 Site of initiation of most recent course of HCV therapy* across Scotland, 2017–18[47]



From Reduction in the population prevalence of hepatitis C virus viraemia among people who inject drugs associated with scale-up of direct-acting anti-viral therapy in community drug services: real-world data - Palmateer - 2021 - Addiction - Wiley Online Library Site of initiation of most recent course of HCV therapy* among people who inject drugs attending injection equipment provision services across Scotland, 2017–18 (data from the Needle Exchange Surveillance Initiative/NESI). GGC = Greater Glasgow and Clyde; GP = general practice; HCV = hepatitis C virus. *Among those who had ever received HCV therapy; †includes needle exchanges, drug treatment sites, community health centres and at an individual's home

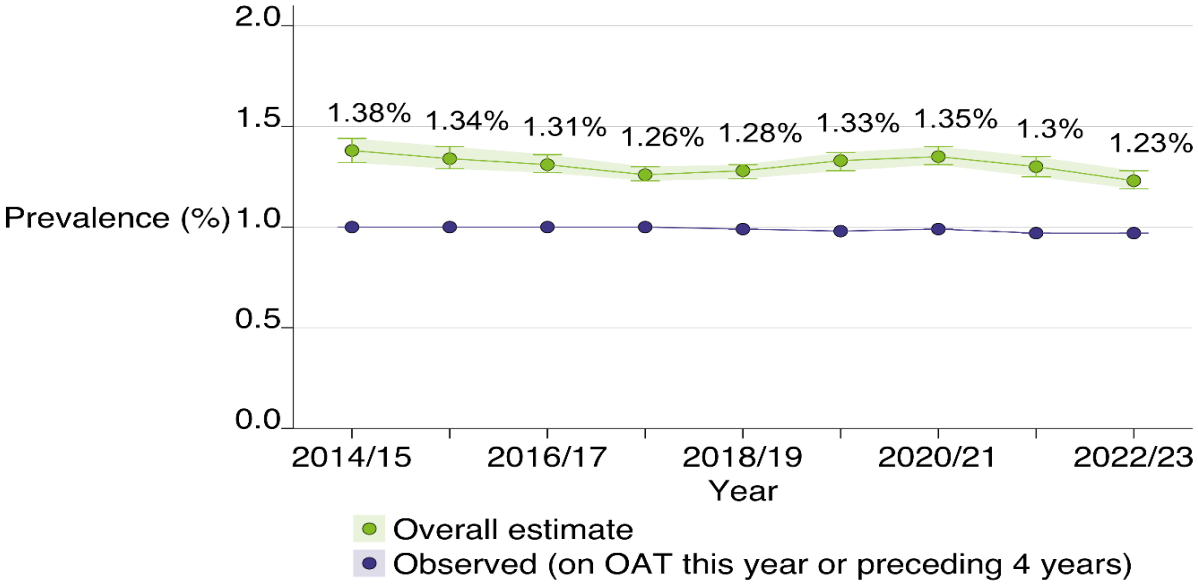
We utilised health related quality of life (QoL) data collected cross-sectionally in NESI and longitudinally as part of WS1. These data show that QoL is profoundly lower in PWID compared to the general population and suggest that QoL was reduced in PWID who were aware of their infection but never treated compared to those unaware of their infection and that improvements in QoL

following successful treatment may be transitory[48]. The evidence corroborates our approach in economic models that have conservative changes in QoL following HCV treatment and highlights importance of averted HCV infections in driving health and economic benefits[31 49].

WS2.2&3 Refining estimates of PWID prevalence & Establishing Virtual Cohort of People in Drug Treatment & Hepatitis Testing and Treatment

A novel method - Multiple Parameter Estimation of Prevalence (MPEP) – was developed that can generate robust estimates of the prevalence of people dependent on opioids and who inject drugs[50 51]. The method utilises the Virtual Cohort – Substance Use and Health Intelligence Linked Dataset (SHIeLD)[52] developed by Public Health Scotland (PHS) which was approved September 2020. Scottish Government now uses MPEP to estimate trends in prevalence of opioid dependence[53] (see figure 3 below from ISD report [54]. In 2022/23 the number of people with opioid dependence in Scotland was estimated to be 43,400 (95% CrI: 41,900 to 45,100) or a prevalence of 1.23% (95% CrI: 1.19% to 1.28%) of 15- to 64-year-olds. There was no evidence of an increase in prevalence since 2014/15. These data are essential for models of HCV (WS4) and interpreting trends in drug related deaths[55]. MPEP has been used in Sydney[50] and is being applied in Wales and piloted in the United States. The cohort has been used in multiple studies of drug related harm, affiliated grants (below) and assessment of HCV treatment on reducing HCV prevalence (WS4).

Figure 3. Estimated prevalence (%) of opioid dependence among the population aged 15-64 years in Scotland; 2014/15 to 2022/23



From ISD report: Estimated Prevalence of Opioid Dependence in Scotland 2014/15 to 2022/23)[54]

Data-linkage of HCV surveillance data in Scotland and in England were used to measure the impact of HCV treatment on extra-hepatic morbidity. In Scotland HCV treatment was associated with a temporary reduced drug related hospital admission rate among PWID but impact (like QoL) on drug related mortality was transient[56]. In England people successfully treated for HCV had a substantially lower risk of mortality than people with HCV that were untreated and some evidence that HCV treatment reduces health inequalities (Simmons & Foster under review).

Linked data were also used to estimate HCV re-infection rates across Scotland – showing that they were higher in people treated in the community and historically increased earlier on in the scale-up of HCV treatment[57]. This study and strategies to improve follow-up of people treated for HCV raised in WS1 and WS3 motivated our PDG (below).

Workstream 3 Qualitative studies – barriers and facilitators to scaling up community-based HCV treatment

We interviewed 40 service providers including peer workers (in seven focus groups and individual interviews), and 31 service users (almost all treated) across the different community pathways in Tayside. We conceptualised the HCV patient pathway in each setting. We generated a behavioural map of the pathway outlining key behavioural steps (from accessing HCV services to completing HCV treatment and ongoing regular HCV testing) through interviews with expert service providers and peer researchers with lived experience of substance use and/or HCV. We then systematically explored facilitators and barriers at each key behavioural step and analysed the data using inductive and deductive reflexive thematic analysis[58]. We then coded identified facilitators and barriers using health behaviour meta frameworks (e.g., the Behaviour Change Wheel[59] and the Theoretical Domains Framework[60] to ensure that resulting recommendations were evidence- and theory-driven. We co-produced the final recommendations with stakeholders (HCV service providers and supporting staff in prison, pharmacies, drug treatment and harm reduction and service users) to generate a sustainable, relevant and useful manual on how to scale-up treatment across the UK. https://www.bristol.ac.uk/media-library/sites/populationhealth/documents/EPIToPe_manual_recommedations_FINAL_VERSION_Sep2021.pdfKey recommendations, applicable to all settings (pharmacy, needle and syringe exchange programme, drug treatment and prison), are listed below. The manual was discussed at multiple workshops with HCV treatment leads in Scotland and England and distributed to the 22 operational delivery networks (ODN) that deliver HCV treatment in England. The manual was endorsed by the Scottish Government and the third sector, and recommendations supported other strategies [61].

Panel: EPIToPE Manual: Recommendations for all settings (i.e. services dealing with people at an increased risk of HCV) when scaling up HCV testing and treatment
Recommendation 1.1: Implement a nurse-led community service model in HCV testing and treatment.
Recommendation 1.2: Establish and maintain a non-judgemental, non-stigmatising, open and inclusive positive service culture
Recommendation 1.3: It is imperative to recruit peer workers, with lived experience of substance misuse, recovery and – if possible – HCV treatment to facilitate service users' engagement with HCV testing and treatment.
Recommendation 1.4: Consider co-locating the HCV treatment setting (i.e. needle and syringe, drug treatment, pharmacy, prison) with a HCV nurse specialist or other qualified HCV health care provider, if possible in the same building or within proximity.
Recommendation 1.5: Provide education for all staff on the benefits and value of HCV testing and treatment
Recommendation 1.6: Enhance education for all staff (i.e. in direct contact with service users) on service users' experience and fear of stigma, including self-stigmatisation, of HCV in diverse treatment settings.
Recommendation 1.7: Implement a drop-in service model to provide opportunistic HCV testing and treatment in line with the availability and the needs of service users.
Recommendation 1.8: Utilise a diverse range of (assertive) outreach or homecare arrangements to enable access and facilitate HCV testing and treatment.

Recommendation 1.9: For all services, ensure commissioning processes detail service level agreements including standard operating procedures (SOPs) or guidelines that facilitate HCV testing and treatment.
Recommendation 1.10: Implement a multiple testing strategy (HCV, HBV, HIV) as part of a wider harm reduction package.
Recommendation 1.11: Minimise the steps in the HCV treatment pathway via the co-ordination of key tasks.
Recommendation 1.12: Consider offering (postal) HCV self-testing kits (e.g. dry blood spot tests) to service users.
Recommendation 1.13: When convenience and speed of HCV testing and treatment are vital, consider implementing point of care (POC) testing
Recommendation 1.14: Ensure that staff responsible for any part of HCV testing and/or treatment in each setting are able to role-share to ensure timely and consistent HCV testing and treatment.
Recommendation 1.15: Ensure staff responsible for any part of HCV testing and/or treatment are able to initiate and conduct an HCV testing conversation at every opportunity.
Recommendation 1.16: Ensure staff responsible for any part of HCV testing and/or treatment are able to conduct dry blood spot tests (DBST) or alternative HCV tests
Recommendation 1.17: Ensure staff responsible for any part of HCV testing and/or treatment respect the service user's preferences in communicating with the HCV nurse specialist or any member of staff working in the HCV service.
Recommendation 1.18: Ensure staff responsible for any part of HCV testing and/or treatment are able to inform and discuss any HCV test results (both, HCV antibodies and HCV PCR) through a package of dedicated training, appraisals and ongoing CPD.
Recommendation 1.19 Ensure staff responsible for any part of HCV testing and/or treatment prioritise referral of the service user to the HCV nurse specialist or other qualified health care professional if further HCV PCR testing or HCV assessment via venepuncture is required.
Recommendation 1.20: Train other qualified health care professional (such as community-based practitioners) to initiate the conversation about finding suitable veins and then to conduct venepuncture on the service user for the HCV PCR blood test.
Recommendation 1.21: Promote the benefits of HCV testing and treatment to service users.
Recommendation 1.22: Provide training on core aspects and the sequence of core aspects in setting up the HCV treatment plan for (new) HCV nurse specialists or other qualified health care professional.
Recommendation 1.23: Co-produce verbal agreements (e.g. behavioural contracts) with service users to assist adherence to HCV treatment, depending on the relationship between service provider and service user.
Recommendation 1.24: Train staff responsible for any part of HCV testing and/or treatment to motivate, support and review the service user during HCV treatment to facilitate treatment adherence.
Recommendation 1.25: View SVR12 testing as an opportunity to promote harm reduction services and thereafter adopt a proactive approach to regular follow-up testing and continuous harm reduction support.
Recommendation 1.26: Implement an HCV Testing and treatment administrative data system.
Recommendation 1.27: Ensure a responsive system is in place to share information across HCV services and patient pathways, for example when a service user disengages from any HCV service.

The local HCV nurse specialist team in Tayside acted as gatekeepers recruiting service users for interviews. Interviews were (co-)facilitated by peer researchers from Scottish Drugs Forum (SDF). There were challenges involving peer researchers in this study, particularly in terms of academic and NHS research processes and governance (research passport, completion of Good Clinical Practice training) which are not designed for peer involvement. While participation in the research was felt to be beneficial by peers, recommendations for future research involving peer researchers were co-developed with SDF and the focus of an international workshop. We also conducted 30 interviews with people who had completed their treatment in the last 12-24 months (average: 18 months) to understand the wider impacts of DAA treatment on people's lives.[62]

There were parallels between key facilitators and barriers to integrating HCV treatment with specialist drug services and a Realist review of OAT and NSP (McCulloch et al., under review). Whereas

integration of services, shared understanding of roles and involvement of peers has been achieved for HCV; optimisation of OAT and NSP was "lagging behind" and there was a gap between current service delivery and good practice as identified in the review.

These studies motivated further qualitative research conducted in WS5 and our PDG (below).

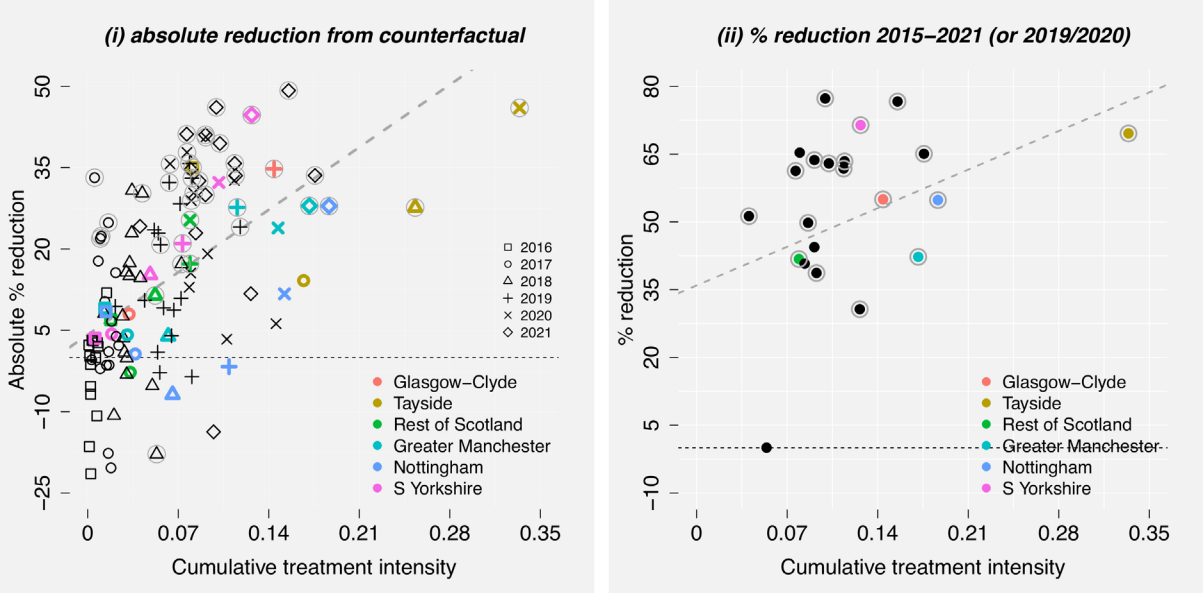
Workstream 4 & 5 Estimating TasP intervention effect and modelling transmission and cost-effectiveness & Evaluating HCV TasP in England

Statistical & Economic Models

We reviewed observational methods for natural experiments and compared synthetic control with cluster RCT methods[63 64]. We showed, in an "emulated" step wedge design across ODN, that peer support increased HCV case-finding and treatment uptake in PWID[65].

We developed a generalised model for evaluating HCV TasP, trends in chronic HCV and the counterfactual (chronic HCV in absence of community scale-up of HCV treatment), using NESI and UAM data[45]. We modelled both the percentage decline in chronic HCV (viraemia) in people who were HCV antibody positive and all PWID tested. The former were more comparable across sites with varying levels of chronic HCV at baseline (pre 2015). The method follows a two-stage approach (aka cut posterior method) fitting trends to the pre-intervention period (2010-2015) and the scale-up period (from 2016); and quantifies TasP as the difference between estimated prevalence and its counterfactual and assesses progress to elimination by comparing most recent prevalence to 2015 baseline. Figure 4A shows clear evidence that intensity of scale-up is associated with reductions in prevalence[45] and updated evidence in Figure 4B shows that Tayside has achieved greater than 80% reduction in chronic HCV (Palmateer et al, under review).

Figure 4A(i&ii) Testing TasP – HCV treatment intensity and reduction in chronic HCV; B – Estimating percentage reduction in chronic HCV from 2015 in Scotland.[66]



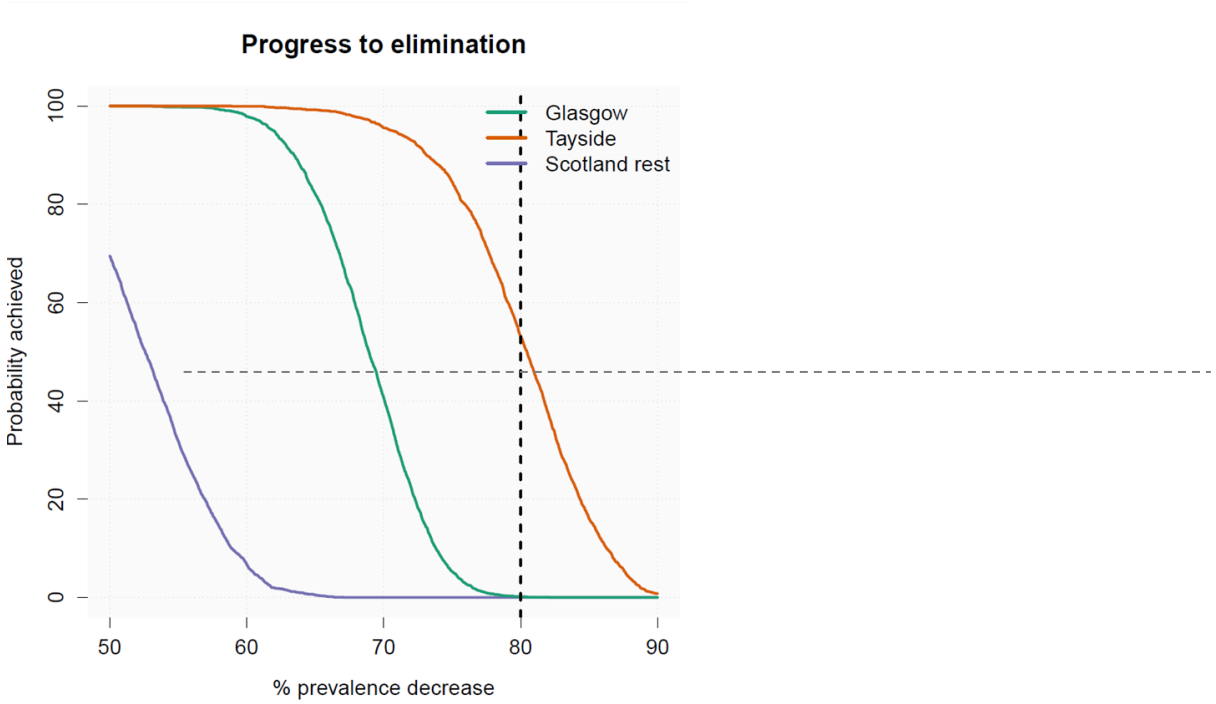


Figure 4A from Evaluating the effect of direct-acting antiviral agent treatment scale-up on Hepatitis C virus prevalence among people who inject drugs in UK - ScienceDirect. Figure 4B is an update.

UAM is underpowered in several ODNs to detect changes in chronic HCV. We, therefore, developed a Bayesian evidence synthesis model that combines UAM data and routine HCV testing data from Sentinel Surveillance BBV system (SSBBV) and stratifies the population into low, medium and high risk (in terms of risk of re-infection). The increase in sample size allows a more flexible approach and more robust evidence on the whole PWID population [Zaouche under review].

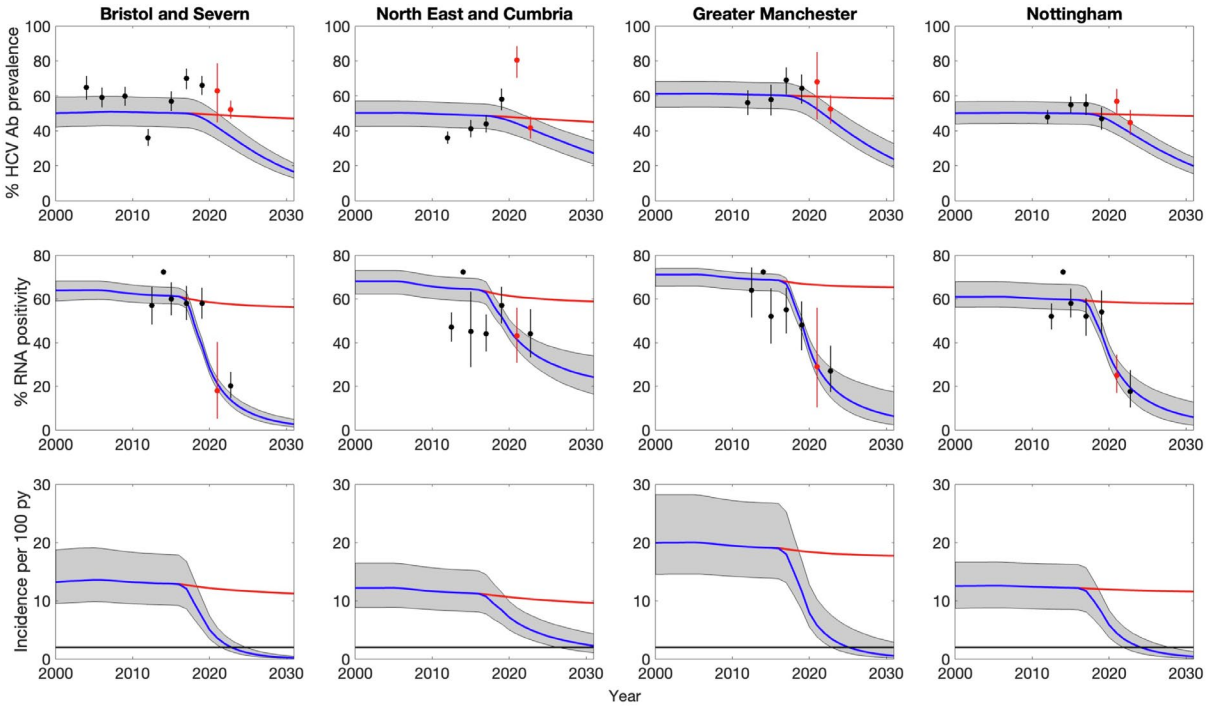
Cost-effectiveness modelling

Multiple pathways in Tayside were shown to be cost-effective[34]. In addition, we showed that the pharmacist-led pathway developed as part of a trial in Tayside is likely to be cost-effective at discounted drug costs[67 68]. As part of HTA affiliated grant we showed that community scale-up of HCV testing and treatment (modelled in 4 ODNs in England) was highly cost-effective[49] at an Incremental Cost Effectiveness Ratio of £308–1609 per QALY. Further if a region was unlikely to meet the WHO elimination target then increasing testing in Drug Treatment Centres (up to 80% tested each year) or prisons (up to 75% tested within their prison stay) was also highly cost-effective. The DAA drug cost negotiated in the UK is commercially sensitive – though likely to be substantially lower than baseline models assuming £10K per course. We extended the economic model to consider under which scenarios investment in scaling up HCV treatment was cost-saving [Ward & Hickman under review]. The majority of savings coming from averted severe liver disease (compensated and decompensated cirrhosis and liver cancer) and averted infections. These projections suggested the scale-up in HCV treatment would be cost saving if the DAA drug cost per person was approximately £2500 or less. It is possible, therefore, that NHS England and Scottish Government investment in HCV treatment was cost-saving and could be cost-saving in future.

Mathematical Modelling

We developed a dynamic deterministic model of HCV transmission among PWID, which incorporated HCV testing and treatment pathways in the community and prison, and incorporated transitions into and out of prison, OAT and high coverage NSP uptake, homelessness status as well as disease progression[49]. The model was initially calibrated to 4 ODN in England and estimated declines in chronic HCV and HCV incidence by 2024 and whether WHO incidence targets were likely to be met by 2030 (summarised in Figure 5). We simplified the model to generate projections for England as a whole, Tayside and Scotland (Kundu et al & Kipkoech et al papers in preparation). The models corroborate the substantial falls in chronic HCV prevalence in Tayside, and project that the WHO elimination targets for HCV incidence among PWID (HCV incidence less than 2 per 100 person years) were met by 2020 (as hypothesised in our protocol – WS1 above). The models also project that England and Scotland are on track, if current HCV treatment rates are maintained, to meet WHO elimination targets by 2030 or earlier. However, the models also highlight that discontinuing HCV treatment could lead to increase in HCV incidence above WHO targets.

Figure 5 Model Projections of HCV Viraemia and HCV Incidence in 4 ODNs



From [Impact and cost-effectiveness of scaling up HCV testing and treatment strategies for achieving HCV elimination among people who inject drugs in England: a mathematical modelling study - The Lancet Regional Health – Europe](). [45] Comparison of model projections among community PWID over time for each ODN against available data for the HCV antibody prevalence (top row), HCV viraemia (HCV RNA) prevalence amongst those with a positive antibody response (middle row), and HCV incidence (bottom row). Projections are shown for the SQ scenario (blue line) and the counterfactual scenario (red line) where there was no scale up in treatment from 2016. Black points are antibody and RNA prevalence estimates that were used in the calibration, which come from the UAM survey (2011–2019), the needs assessment (2022) and sentinel surveillance (only RNA prevalence in 2014). Additional antibody prevalence estimates for Bristol come from three community surveys of PWID (2004–2009). Red points are HCV RNA and antibody prevalence estimates from the UAM survey for 2020–2021 and antibody prevalence estimates from the needs assessment (2022) that were not used in the model calibration.

Other Modelling

The UAM has also been used to measure how the HCV case cascade has changed over time – which is critical to our models[69 70]. In Scotland it has been possible to create a virtual cohort of all people known to be opioid dependent/PWID and track the proportion tested and treated for HCV – and show that missing observations are associated with lower risk [51]. NESI also has been used to estimate and track incidence of primary infection and re-infection rates over time in a high risk population across Scotland[71]. Statistical and mathematical models were presented at Viral Hepatitis C Elimination Modelling and contribute to UK evidence on assessing the impact of HCV TasP. We also summarised all models that can be used to estimate directly or indirectly changes in HCV incidence in UK and progress towards WHO HCV elimination targets[72]. These will be discussed in a meeting coordinated by UKHSA and supported by EPIToPe to decide if and when UK will prepare document on "pathways towards HCV elimination" for review by WHO.

WS5 Qualitative Evidence

In WS5 we conducted a further qualitative study, drawing upon Normalisation Process Theory (NPT)[73] to evaluate the intensive scale up of testing and treatment in England. We conducted semi-structured interviews with a range of staff (n=28) recruited from services across the same four ODNs that were included in the mathematical modelling in WS4[49]. Our participants reported that testing and treatment has become normalised practice in many community settings, and this adoption into everyday practice can be seen in the success of the scale up. However, implementation was not possible in all settings, some drug treatment teams were unable to incorporate this into their workload, and unlike in Scotland, community pharmacies, were unable to hold and supply the DAA treatment, limiting their ability to engage in scaled up testing and treatment. The impact of this was mitigated through ODN managers coordinating mass testing events in areas where testing and treatment rates were lagging. In line with the qualitative findings in WS3, peer workers were key to engaging and supporting people through the testing and treatment pathway. Where the digital infrastructure lagged behind, they were also vital links between services, enabling teams to keep track of who still needed testing and treatment. (McCulloch et al., under review).

Programme Development Grant (PDG)– PROACTIVE (HePatitis C Reinfection: Optimising surveillAnCe for detection and preVEntion)

In the PDG (due to complete 31/03/26) we are conducting a qualitative study, to inform the next phase of HCV care for PWID and how services are shifting their focus to monitoring for and preventing reinfection. We are working with 4 services (two in Scotland and two in England) and people with lived and living experience to develop recommendations for optimising annual (or more intensive) follow-up testing for PWID who have received DAA treatment.

Patient and Public Involvement

The Hepatitis C Trust and the Scottish Drug Forum (SDF) were actively involved in the development of EPIToPe and the EPIToPe study steering group. SDF co-led qualitative research assessing barriers and facilitators to HCV treatment access, supporting peer researcher training and contributing to the development of recommendations for our forthcoming paper on future peer researcher training and

support. The Hepatitis C Trust supported evaluation of peer support and barriers and facilitators of HCV treatment scale-up in England. The input from PPI groups has influenced the design of care pathways and has ensured that peer research is an essential element of the qualitative strand of EPIToPe. This strong peer engagement throughout EPIToPe continues in new grants and projects led by EPIToPe team members, e.g. for our PDG the study team joined by co-applicant Rebecca Bulmer: Hepatitis C Trust Peer Researcher, has taken an active role in the design and delivery of the research as well as being our "person on the ground" giving us fortnightly updates on her experiences providing HCV support and outreach NSP in her region. Her time with the project has inspired Rebecca to undertake further formal research training – attending a course with the Royal College of London (Titled: Practical guide to peer and community research). Rebecca has also since been appointed as an advisor to other studies conducting HCV research.

Funding statement: 'This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Reference Number RP-PG-0616-20008). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.In addition, we acknowledge support from our steering committee (appendix), UKHSA, Public Health Scotland, NIHR Health Protection Research Unit in Evaluation, and the Bristol.NM is supported by the National Institute for Drug Abuse [grant number R01 DA037773] and the University of California San Diego Center for AIDS Research (CFAR), a National Institute of Health (NIH) funded program [grant number P30 AI036214].

We would like to thank all those involved in PPI from both SDF and the Hepatitis C Trust.

Supplement:- Steering Committee Members; Affiliated Grants; EPIToPe Publications

EPIToPe Steering Group
Prof Geoffrey Dusheiko (Chair)
Dr Prun Bijral
Prof Marie-Claude Boily
Dr Nicola Steedman
Paul Linton
Prof Bianca De Stavola
Dr Claire Foreman
Prof Will Irving
Stuart Smith
Gill Hawkins
Beatrice Emmanouil
Mark Gillyon-Powell
Petra Wright
Sylvia Fox

Additional/affiliated Grants

A number of the EPIToPe research team are part of a team that have been awarded a grant affiliated to EPIToPe and compliments the work planned evaluating TasP and/or utilising virtual cohort for evaluating public health interventions:-

1. McAuley A, et al. Title: Evaluating the impact of public health interventions in Scotland's Drug-Related Death epidemic, Scottish Government (DDTFRF08), January 2021 to June 2022, £99,997
2. Munro A, MacGillivray S, Gilchrist G, Neale J, Hickman M, Vickeman P, Maxwell M, Matheson C. Title: Understanding the contextual factors that impact on the effective provision of opiate substitution therapy (OST) and needle and syringe programmes (NSP) in the UK: a multi-method study and realist evaluation of what works, for whom and under what circumstances. NIHR HTA (NIHR129798) Dec 2020 – November 2022 £621,704
3. Vickerman P, Hickman M, Miners A, Mandal S, Foster G, Kesten J, Brown A, Ustianowski A, Gordon F, Ryder S. A comprehensive model and economic evaluation of HCV elimination amongst people who inject drugs in England to guide case-finding intervention policy and implementation. NIHR (HTA 128513). Jan 2020-Dec 2022 £411,401.97
4. Palmateer N et al. Prevention and control of infectious diseases among people who inject drugs (CT.19.EU4MD.0099.1.0), April 2020-March 2021, £30,000
5. Pantellis S, Towards realistic methods for evaluating public health interventions using time-series data, UKRI Medical Research Council Career Development Award (G UKRI332), Feb 2025-Jan 2030, £1,415,424.33.
6. De Angelis D, MRC Work Programme Lead, MRC BSU Programme on Population Health (£3.5M)
7. Degenhardt L (CoPI), Hickman M (CoPI), Martin N (CoPI), Hutchinson SJ, et al. Transforming the evidence base on estimating prevalence of problem drug use and evaluating impact of interventions to prevent drug related harm: a multi-jurisdictional data linkage study (TRANSFORM) (NIH, 2025-2029, £2.9 million)
8. Hutchinson SJ (co-PI), Hickman M, et al. Evaluating the impact of the UK's first Sanctioned Safer Drug Consumption Facility: A mixed-methods natural experiment study (ENACT - NIHR207273) (2025-2029, £3.1 million) NIHR PDG on drug consumption rooms – modelling output
9. Stone J (CoPI), Hickman M (co-PI), Hutchinson SJ, et al. Evaluating the Impact of Interventions for the Prevention of Drug-related Deaths in the Population in Scotland (EPhesuS) (NIHR-160569 PDG grant, £1.3million)
10. Family, H., Bulmer, R., McCulloch, P., Whiteley, D., Horwood, J., Hutchinson, S., & Hickman, M. hePatitis c Reinfection: Optimising surveillAnCe for deTectIon and prevention (PROACTIVE) (NIHR-207646 PDG, £141,778.29)

EPIToPE and Affiliated Projects References (Published/ in press)

1. Harris RJ, Harris HE, Mandal S, Ramsay M, Vickerman P, Hickman M, et al. Monitoring the hepatitis C epidemic in England and evaluating intervention scale-up using routinely collected data. Journal of Viral Hepatitis. 2019;26(5):541-51.
2. Hickman M, Dillon JF, Elliott L, De Angelis D, Vickerman P, Foster G, et al. Evaluating the population impact of hepatitis C direct acting antiviral treatment as prevention for people who inject drugs (EPIToPe) – a natural experiment (protocol). BMJ Open. 2019;9(9):e029538.

3. Samartsidis P, Seaman SR, Presanis AM, Hickman M, De Angelis D. Assessing the Causal Effect of Binary Interventions from Observational Panel Data with Few Treated Units. Statistical Science. 2019;34(3):486-503, 18.
4. Jones HE, Harris RJ, Downing BC, Pierce M, Millar T, Ades AE, et al. Estimating the prevalence of problem drug use from drug-related mortality data. Addiction. 2020;115(12):2393-404.
5. Roberts K.; MacLeod J.; Metcalfe C.; Hollingworth W.; Williams J.; Muir P.; Vickerman P.; Clement C.; Gordon F.; Irving W.; Waldron C.-A.; North P.; Moore P.; Simmons R.; Miners A.; Horwood J.; Hickman M. Cost effectiveness of an intervention to increase uptake of hepatitis C virus testing and treatment (HepCATT): Cluster randomised controlled trial in primary care. 2020 The BMJ; 368: -10.1136/bmj.m322
6. Bardsley M, Heinsbroek E, Harris R, Croxford S, Edmundson C, Hope V, et al. The impact of direct-acting antivirals on hepatitis C viraemia among people who inject drugs in England; real-world data 2011–2018. Journal of Viral Hepatitis. 2021;28(10):1452-63.
7. EPIToPe. Evidence-based and Theoretically informed Recommendations for Scaling up HCV Testing and Treatment for People Who Inject Drugs. Bristol; 2021. https://www.gcu.ac.uk/__data/assets/pdf_file/0019/38350/epitope_manual_recommedations_final_version_sep2021.pdf
8. Palmateer NE, McAuley A, Dillon JF, McDonald S, Yeung A, Smith S, et al. Reduction in the population prevalence of hepatitis C virus viraemia among people who inject drugs associated with scale-up of direct-acting anti-viral therapy in community drug services: real-world data. Addiction. 2021;116(10):2893-907.
9. Samartsidis P, Martin NN, De Gruttola V, De Vocht F, Hutchinson S, Lok JJ, et al. Evaluating the power of the causal impact method in observational studies of HCV treatment as prevention. Stat Commun Infect Dis. 2021;13(1):20200005.
10. Samartsidis P, Seaman SR, Montagna S, Charlett A, Hickman M, De Angelis D. A Bayesian multivariate factor analysis model for evaluating an intervention by using observational time series data on multiple outcomes. J R Stat Soc Ser A Stat Soc. 2021;28(1):155-66.
11. Byrne CJ, Beer L, Inglis SK, Robinson E, Radley A, Goldberg DJ, et al. Real-world outcomes of rapid regional hepatitis C virus treatment scale-up among people who inject drugs in Tayside, Scotland. Aliment Pharmacol Ther. 2022;55(5):568-79.
12. Jugnarain DV, Halford R, Smith S, Hickman M, Samartsidis P, Foster GR. Role of peer support in a hepatitis C elimination programme. Journal of Viral Hepatitis. 2022;29(1):43-51.
13. Myring G, Lim AG, Hollingworth W, McLeod H, Beer L, Vickerman P, et al. Cost-effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for hepatitis C in patients receiving opioid substitution therapy: An economic evaluation alongside a pragmatic cluster randomised trial. J Infect. 2022;85(6):676-82.
14. Yeung A, Palmateer NE, Dillon JF, McDonald SA, Smith S, Barclay S, et al. Population-level estimates of hepatitis C reinfection post scale-up of direct-acting antivirals among people who inject drugs. Journal of Hepatology. 2022;76(3):549-57.
15. McAuley A, Fraser R, Glancy M, Yeung A, Jones HE, Vickerman P, et al. Mortality among individuals prescribed opioid-agonist therapy in Scotland, UK, 2011–20: a national retrospective cohort study. The Lancet Public Health. 2023;8(7):e484-e93.
16. McDonald SA, Myring G, Palmateer NE, McAuley A, Beer L, Dillon JF, et al. Improved health-related quality of life after hepatitis C viraemic clearance among people who inject drugs may not be durable. Addiction. 2023;118(7):1340-50.

17. Robinson E, Byrne CJ, Carberry J, Radley A, Beer LJ, Inglis SK, et al. Laying the foundations for hepatitis C elimination: evaluating the development and contribution of community care pathways to diagnostic efforts. BMC Public Health. 2023;23(1):54.
18. Ward Z, Fraser H, Trickey A, Kesten J, Gibson A, Reid L, et al. FRI-165 - A modelling study of the impact of scaling up of HCV case finding and treatment for people who inject drugs in English region of Bristol and Severn. Journal of Hepatology. 2023;78:S909.
19. Allen LI, Fraser H, Stone J, McAuley A, Trayner KMA, Metcalfe R, et al. Testing and Treatment Interventions in Community Settings Key to Controlling a Recent Human Immunodeficiency Virus Outbreak Among People Who Inject Drugs in Glasgow: A Modeling Study. The Journal of Infectious Diseases. 2024;230(1):e48-e59.
20. Gliddon HD, Ward Z, Heinsbroek E, Croxford S, Edmundson C, Hope VD, et al. Has the HCV cascade of care changed among people who inject drugs in England since the introduction of direct-acting antivirals? International Journal of Drug Policy. 2024:104324.
21. Markoulidakis A, Hickman M, McAuley A, Barnsdale LR, Welton NJ, Glancy M, et al. Prevalence of opioid dependence in Scotland 2015–2020: A multi-parameter estimation of prevalence (MPEP) study. Addiction. 2024;119(8):1410-20.
22. McDonald SA, Hickman M, Dillon JF, Yeung A, McAuley A, Fraser A, et al. A transient positive association between direct-acting antiviral therapy for hepatitis C infection and drug-related hospitalization among people who inject drugs: Self-controlled case-series analysis of national data. Addiction. 2024;119(2):369-78.
23. Samartsidis P, Harris RJ, Dillon J, Desai M, Foster GR, Gunson R, et al. Evaluating the effect of direct-acting antiviral agent treatment scale-up on Hepatitis C virus prevalence among people who inject drugs in UK. Int J Drug Policy. 2025:104429.
24. Vojt G, Elliott L, Family H, Sharkey C, Stephens B, Hutchinson SJ, Hickman M, et al. Post-treatment life-trajectories among people who inject drugs who completed hepatitis C treatment with direct acting antivirals: a thematic analysis. Br J Health Psychol. 2025 Sep;30(3):e70005.
25. Simmons R, Powell AA, Ijaz S, Mandal S, Shute J, Mohammadi Y, Lattimore M, McOwat K, Moore HL, O'Rourke A, Desai M, Macleod J, Asgharzadeh A, Ward Z, Vickerman P, Harris RJ, Foster GR, Roberts K, Hickman M. Pilot postal birth cohort hepatitis C virus screening in UK primary care: HepCAPP study. Br J Gen Pract. 2025;75:e122-e128.
26. Mitchell H, Clancy I, De Angelis D, Egan C, Harris R, Hutchinson S, Samartsidis P, Vickerman P, Ward Z, Yeung A, Zaouche M, Hibbert M, Emmanouil B, McAuley A, Nugenth C, Smith J, Artenie A, Desai M, Hickman M. Using modelling and public health surveillance data to evidence progress towards the WHO incidence target for hepatitis C elimination in people who inject drugs - a review of complementary approaches in the United Kingdom. Int J Drug Policy. 2025: 105059
27. McDonald SA, Palmateer N, McAuley A, Gunson RN, Barclay ST, Dillon JF, Hickman M, Hutchinson SJ. Estimating the incidence rates of primary infection and reinfection with hepatitis C virus among people who inject drugs in Scotland: a model-based analysis of repeated cross-sectional survey data. Lancet Reg Health Eur. 2026, 60: 101505
28. Ward Z, Simmons R, Fraser H, et al. Impact and cost-effectiveness of scaling up HCV testing and treatment strategies for achieving HCV elimination among people who inject drugs in England: a mathematical modelling study. *Lancet Reg Health Eur* 2025;49:101176. doi: 10.1016/j.lanepe.2024.101176 [published Online First: 20241212]

Papers under review / in preparation

1. Kundu B et al. Estimating the impact of scaling up hepatitis C virus treatment among people who inject drugs in Tayside and all of Scotland (in preparation)
2. Kipkoech K et al. Estimating the impact of scaling up HCV treatment in community and prison in England (in preparation)
3. McCulloch P, Family H, Johnson D, Vojt G, Lancaster K, Vickerman P; Hutchinson S, Hickman M, Horwood J. Scale-up and normalisation of hepatitis C testing and treatment for people who inject drugs in England: A qualitative process evaluation. (under review)
4. Palmateer NE, Samartsidis P, Biggam C, McAuley A, McDonald SA, Dillon J, Barclay S, Samantha Shepherd S, Gunson R, McCormick D, De Angelis D, Hickman M, Hutchinson SJ. Impact of direct-acting antiviral therapy scale-up among people who inject drugs in Scotland: regional evidence of Hepatitis C virus elimination. (under review)
5. Simmons, R., Desai, M., Mandal, S., Hickman, M., Harris, R.J., Gillyon-Powell, M., Emmanouil, B., Foster, G.R. (Under Review) Impact on mortality of a national program of supported, active care in the treatment of marginalised people with chronic HCV infection.
6. Vojt, G et al (under review) What can be learned from the whole system scale up of hepatitis C care? A qualitative process evaluation.
7. Fraser H, Mc Pherson S, Ryder S, Gordon F, Vilar J, Mandal S, Foster G, Gillyon-Powell M, Dillon J, Hutchinson S, Vickerman P, Hickman M. Can scaling up HCV treatment in People Who Inject Drugs be cost-saving: an economic modelling study for England. (under review)
8. Yeung A, et al. Estimating hepatitis C prevalence and incidence among those attending drug services in Scotland: a national retrospective cohort study. (in preparation)
9. Zaouche M, Desai M, Family H, Harris RJ, Mitchell H, Rue H, Samartsidis P, et al. Estimating trends in hepatitis C virus prevalence among people who inject drugs in England using multiple data sources. (under review)
10. Ward Z, Fraser H, Mc Pherson S, Ryder S, Gordon F, Vilar J, Mandal S, Foster G, Gillyon-Powell M, Dillon J, Hutchinson S, Vickerman P, Hickman M. Can scaling up HCV treatment in People Who Inject Drugs be cost-saving: an economic modelling study for England (under review)

References (cited in report)

1. Williams R, Aspinall R, Bellis M, et al. Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. *Lancet* 2014;384(9958):1953-97. doi: 10.1016/S0140-6736(14)61838-9
2. World Health Organization. Consolidated guidelines on person-centred viral hepatitis strategic information: using data to support country scale-up of hepatitis prevention, diagnosis and treatment services. Geneva: World Health Organization, 2024.
3. World Health Organization. Guidance for country validation of viral hepatitis elimination and path to elimination: technical report. Geneva: World Health Organization, 2023.
4. De Angelis D, Sweeting M, Ades A, et al. An evidence synthesis approach to estimating Hepatitis C prevalence in England and Wales. *Stat Methods Med Res* 2009;18(4):361-79. doi: 0962280208094691 [pii];10.1177/0962280208094691 [doi]
5. Harris RJ, Ramsay M, Hope VD, et al. Hepatitis C prevalence in England remains low and varies by ethnicity: an updated evidence synthesis. *Eur J Public Health* 2012;22(2):187-92. doi: ckr083 [pii];10.1093/eurpub/ckr083 [doi]
6. Hutchinson SJ, Roy KM, Wadd S, et al. Hepatitis C virus infection in Scotland: epidemiological review and public health challenges. *Scott Med J* 2006;51(2):8-15.

7. Prevost TC, Presanis AM, Taylor A, et al. Estimating the number of people with hepatitis C virus who have ever injected drugs and have yet to be diagnosed: an evidence synthesis approach for Scotland. *Addiction* 2015;110(8):1287-300. doi: 10.1111/add.12948
8. Hutchinson SJ, McIntyre PG, Molyneaux P, et al. Prevalence of hepatitis C among injectors in Scotland 1989-2000: declining trends among young injectors halt in the late 1990s. *Epidemiol Infect* 2002;128(3):473-77.
9. Martin NK, Foster GR, Vilar J, et al. HCV treatment rates and sustained viral response among people who inject drugs in seven UK sites: real world results and modelling of treatment impact. *J Viral Hepat* 2015;22(4):399. doi: 10.1111/jvh.12338
10. McLeod A, Weir A, Aitken C, et al. Rise in testing and diagnosis associated with Scotland's Action Plan on Hepatitis C and introduction of dried blood spot testing. *J Epidemiol Community Health* 2014;68(12):1182-8. doi: 10.1136/jech-2014-204451
11. Palmateer NE, Hutchinson SJ, Innes H, et al. Review and meta-analysis of the association between self-reported sharing of needles/syringes and hepatitis C virus prevalence and incidence among people who inject drugs in Europe. *IntJDrug Policy* 2013;24(2):85-100. doi: S0955-3959(12)00123-5 [pii];10.1016/j.drugpo.2012.08.006 [doi]
12. Palmateer NE, Taylor A, Goldberg DJ, et al. Rapid decline in HCV incidence among people who inject drugs associated with national scale-up in coverage of a combination of harm reduction interventions. *PLoS One* 2014;9(8):e104515. doi: 10.1371/journal.pone.0104515
13. Roy KM, Hutchinson SJ, Wadd S, et al. Hepatitis C virus infection among injecting drug users in Scotland: a review of prevalence and incidence data and the methods used to generate them. *Epidemiol Infect* 2007;135(3):433-42.
14. Harris RJ, Hope VD, Morongiu A, et al. Spatial mapping of hepatitis C prevalence in recent injecting drug users in contact with services. *Epidemiol Infect* 2011:1-10. doi: S0950268811001634 [pii];10.1017/S0950268811001634 [doi]
15. Hickman M, Hope V, Brady T, et al. Hepatitis C virus (HCV) prevalence, and injecting risk behaviour in multiple sites in England in 2004. *Journal of viral hepatitis* 2007;14(9):645-52.
16. Hope VD, Hickman M, Ngui SL, et al. Measuring the incidence, prevalence and genetic relatedness of hepatitis C infections among a community recruited sample of injecting drug users, using dried blood spots. *J Viral Hepat* 2011;18:262-70. doi: JVH1297 [pii];10.1111/j.1365-2893.2010.01297.x [doi]
17. Sutton AJ, Gay NJ, Edmunds WJ, et al. Modelling the force of infection for hepatitis B and hepatitis C in injecting drug users in England and Wales. *BMC InfectDis* 2006;6:93. doi: 1471-2334-6-93 [pii];10.1186/1471-2334-6-93 [doi]
18. Sweeting MJ, Hope VD, Hickman M, et al. Hepatitis C infection among injecting drug users in England and Wales (1992-2006): there and back again? *Am J Epidemiol* 2009;170(3):352-60. doi: kwp141 [pii];10.1093/aje/kwp141 [doi]
19. Turner KM, Hutchinson S, Vickerman P, et al. The impact of needle and syringe provision and opiate substitution therapy on the incidence of hepatitis C virus in injecting drug users: pooling of UK evidence. *Addiction* 2011;106(11):1978-88. doi: 10.1111/j.1360-0443.2011.03515.x [doi]
20. Van Den Berg C, Smit C, Van BG, et al. Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users. *Addiction* 2007;102(9):1454-62. doi: ADD1912 [pii];10.1111/j.1360-0443.2007.01912.x [doi]
21. Hagan H, Pouget ER, Des Jarlais DC. A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs. *J InfectDis* 2011;204(1):74-83. doi: jir196 [pii];10.1093/infdis/jir196 [doi]
22. Platt L, Reed J, Minozzi S, et al. Effectiveness of needle/syringe programmes and opiate substitution therapy in preventing HCV transmission among people who inject drugs. *Cochrane Database Syst Rev* 2016;2016(1) doi: 10.1002/14651858.CD012021

23. de Vos AS, van der Helm JJ, Matser A, et al. Decline in incidence of HIV and hepatitis C virus infection among injecting drug users in Amsterdam; evidence for harm reduction? *Addiction* 2013;108(6):1070-81. doi: 10.1111/add.12125
24. Vickerman P, Martin N, Turner K, et al. Can needle and syringe programmes and opiate substitution therapy achieve substantial reductions in hepatitis C virus prevalence? Model projections for different epidemic settings. *Addiction* 2012;107(11):1984-95. doi: 10.1111/j.1360-0443.2012.03932.x [doi]
25. Hellard M, Doyle JS, Sacks-Davis R, et al. Eradication of hepatitis C infection: The importance of targeting people who inject drugs. *Hepatology* 2014;59(2):366-69. doi: 10.1002/hep.26623
26. Hagan LM, Wolpe PR, Schinazi RF. Treatment as prevention and cure towards global eradication of hepatitis C virus. *Trends in Microbiology* 2013;21(12):625-33. doi: http://dx.doi.org/10.1016/j.tim.2013.09.008
27. Grebely J, Matthews GV, Lloyd AR, et al. Elimination of hepatitis C virus infection among people who inject drugs through treatment as prevention: feasibility and future requirements. *Clin Infect Dis* 2013;57(7):1014-20. doi: 10.1093/cid/cit377
28. Bruggmann P. Treatment as prevention: The breaking of taboos is required in the fight against hepatitis C among people who inject drugs. *Hepatology* 2013;58(5):1523-25. doi: 10.1002/hep.26539
29. Martin NK, Vickerman P, Grebely J, et al. HCV treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology* 2013 doi: 10.1002/hep.26431 [doi]
30. Wedemeyer H, Duberg AS, Buti M, et al. Strategies to manage hepatitis C virus (HCV) disease burden. *Journal of viral hepatitis* 2014;21 Suppl 1:60-89. doi: 10.1111/jvh.12249
31. Martin NK, Vickerman P, Dore GJ, et al. Prioritization of HCV treatment in the direct-acting antiviral era: An economic evaluation. *J Hepatol* 2016;65(1):17-25. doi: 10.1016/j.jhep.2016.02.007
32. Fraser H, Martin NK, Brummer-Korvenkontio H, et al. Model projections on the impact of HCV treatment in the prevention of HCV transmission among people who inject drugs in Europe. *J Hepatol* 2018;68(3):402-11. doi: 10.1016/j.jhep.2017.10.010 [published Online First: 2017/10/31]
33. Jafferbhoy H, Miller MH, Dunbar JK, et al. Intravenous drug use: not a barrier to achieving a sustained virological response in HCV infection. *J Viral Hepat* 2012;19(2):112-9. doi: 10.1111/j.1365-2893.2011.01446.x
34. Manca F, Robinson E, Dillon JF, et al. Eradicating hepatitis C: Are novel screening strategies for people who inject drugs cost-effective? *Int J Drug Policy* 2020;82:102811. doi: 10.1016/j.drugpo.2020.102811 [published Online First: 20200622]
35. Hickman M, Dillon JF, Elliott L, et al. Evaluating the population impact of hepatitis C direct acting antiviral treatment as prevention for people who inject drugs (EPIToPe) - a natural experiment (protocol). *BMJ Open* 2019;9(9):e029538. doi: 10.1136/bmjopen-2019-029538 [published Online First: 2019/09/26]
36. Dillon J, Hayes P, Barclay S, et al. National Clinical Guidelines for the treatment of HCV in adults (version 5) 2018 [Available from: https://publichealthscotland.scot/media/23268/2018-06-national-clinical-guidelines-treatment-hepatitis-c-in-adults.pdf.
37. Byrne CJ, Beer L, Inglis SK, et al. Real-world outcomes of rapid regional hepatitis C virus treatment scale-up among people who inject drugs in Tayside, Scotland. *Aliment Pharmacol Ther* 2022;55(5):568-79. doi: 10.1111/apt.16728 [published Online First: 2021/12/09]
38. Palmateer NE, McAuley A, Dillon JF, et al. Reduction in the population prevalence of hepatitis C virus viraemia among people who inject drugs associated with scale-up of direct-acting anti-viral therapy in community drug services: real-world data. *Addiction* 2021;116(10):2893-907. doi: 10.1111/add.15459 [published Online First: 2021/03/03]

39. Robinson E, Byrne CJ, Carberry J, et al. Laying the foundations for hepatitis C elimination: evaluating the development and contribution of community care pathways to diagnostic efforts. *BMC Public Health* 2023;23(1):54. doi: 10.1186/s12889-022-14911-1 [published Online First: 20230107]
40. England PH. Hepatitis C in the UK 2016 report: Working towards its elimination as a major public health threat. In: Harris HE, ed. London: Public Health England, 2016.
41. Health Protection Scotland UotWoS, Glasgow Caledonian University and the West of Scotland Specialist Virology Centre. The Needle Exchange Surveillance Initiative: Prevalence of blood-borne viruses and injecting risk behaviours among people who inject drugs attending injecting equipment provision services in Scotland, 2008-09 to 2015-16. In: Scotland HP, ed. Glasgow, 2017.
42. Brant LJ, Hurrelle M, Balogun MA, et al. Sentinel laboratory surveillance of hepatitis C antibody testing in England: understanding the epidemiology of HCV infection. *Epidemiol Infect* 2007;135(3):417-26. doi: 10.1017/S0950268806006832
43. Brant LJ, Hurrelle M, Balogun MA, et al. Where are people being tested for anti-HCV in England? Results from sentinel laboratory surveillance. *Journal of viral hepatitis* 2008;15(10):729-39. doi: 10.1111/j.1365-2893.2008.01000.x
44. Lattimore S, Irving W, Collins S, et al. Using surveillance data to determine treatment rates and outcomes for patients with chronic hepatitis C virus infection. *Hepatology* 2014;59(4):1343-50. doi: 10.1002/hep.26926
45. Samartsidis P, Harris RJ, Dillon J, et al. Evaluating the effect of direct-acting antiviral agent treatment scale-up on Hepatitis C virus prevalence among people who inject drugs in UK. *Int J Drug Policy* 2024:104429. doi: 10.1016/j.drugpo.2024.104429 [published Online First: 20240627]
46. Bardsley M, Heinsbroek E, Harris R, et al. The impact of direct-acting antivirals on hepatitis C viraemia among people who inject drugs in England; real-world data 2011-2018. *Journal of viral hepatitis* 2021;28(10):1452-63. doi: 10.1111/jvh.13575 [published Online First: 2021/07/17]
47. !!! INVALID CITATION !!! 35
48. McDonald SA, Myring G, Palmateer NE, et al. Improved health-related quality of life after hepatitis C viraemic clearance among people who inject drugs may not be durable. *Addiction* 2023;118(7):1340-50. doi: 10.1111/add.16169 [published Online First: 20230316]
49. Ward Z, Simmons R, Fraser H, et al. Impact and cost-effectiveness of scaling up HCV testing and treatment strategies for achieving HCV elimination among people who inject drugs in England: a mathematical modelling study. *Lancet Reg Health Eur* 2025;49:101176. doi: 10.1016/j.lanepe.2024.101176 [published Online First: 20241212]
50. Downing BC, Hickman M, Jones NR, et al. Prevalence of opioid dependence in New South Wales, Australia, 2014-16: Indirect estimation from multiple data sources using a Bayesian approach. *Addiction* 2023;118(10):1994-2006. doi: 10.1111/add.16268 [published Online First: 20230608]
51. Jones HE, Harris RJ, Downing BC, et al. Estimating the prevalence of problem drug use from drug-related mortality data. *Addiction* 2020;115(12):2393-404. doi: 10.1111/add.15111 [published Online First: 20200609]
52. Public Health Scotland. Substance Use and Health Intelligence Linked Dataset (SHIeLD) [Available from: https://publichealthscotland.scot/population-health/improving-scotlands-health/drugs/data-and-intelligence/substance-use-and-health-intelligence-linked-dataset-shield/.
53. Markoulidakis A, Hickman M, McAuley A, et al. Prevalence of opioid dependence in Scotland 2015-2020: A multi-parameter estimation of prevalence (MPEP) study. *Addiction* 2024;119(8):1410-20. doi: 10.1111/add.16500 [published Online First: 20240417]

54. Public Health Scotland. Estimated Prevalence of Opioid Dependence in Scotland 2014/15 to 2022/23: Public Health Scotland; 2025 [Available from: https://publichealthscotland.scot/publications/estimated-prevalence-of-opioid-dependence-in-scotland/estimated-prevalence-of-opioid-dependence-in-scotland-201415-to-202223/#:~:text=The%20estimated%20number%20of%20people%20with%20opioid%20dependence,CrI%3A%201.19%25%20to%201.28%25%29%20of%2015-%20to%2064-year-olds.
55. McAuley A, Fraser R, Glancy M, et al. Mortality among individuals prescribed opioid-agonist therapy in Scotland, UK, 2011-20: a national retrospective cohort study. *Lancet Public Health* 2023;8(7):e484-e93. doi: 10.1016/S2468-2667(23)00082-8 [published Online First: 20230607]
56. McDonald SA, Hickman M, Dillon JF, et al. A transient positive association between direct-acting antiviral therapy for hepatitis C infection and drug-related hospitalization among people who inject drugs: Self-controlled case-series analysis of national data. *Addiction* 2024;119(2):369-78. doi: 10.1111/add.16344 [published Online First: 20230919]
57. Yeung A, Palmateer NE, Dillon JF, et al. Population-level estimates of hepatitis C reinfection post scale-up of direct-acting antivirals among people who inject drugs. *J Hepatol* 2022;76(3):549-57. doi: 10.1016/j.jhep.2021.09.038 [published Online First: 2021/10/12]
58. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology* 2006;3(2):77-101. doi: 10.1191/1478088706qp063oa
59. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci* 2011;6:42. doi: 10.1186/1748-5908-6-42 [published Online First: 20110423]
60. Atkins L, Francis J, Islam R, et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. *Implement Sci* 2017;12(1):77. doi: 10.1186/s13012-017-0605-9 [published Online First: 20170621]
61. Scottish Government. Reset and Rebuild: A Recovery Plan for Sexual Health and Blood Borne Virus Services Edinburgh: The Scottish Government; 2021 [Available from: https://www.gov.scot/binaries/content/documents/govscot/publications/strategy-plan/2021/08/reset-rebuild-recovery-plan-sexual-health-blood-borne-virus-services/documents/reset-rebuild-recovery-plan-sexual-health-blood-borne-virus-services/reset-rebuild-recovery-plan-sexual-health-blood-borne-virus-services/govscot%3Adocument/reset-rebuild-recovery-plan-sexual-health-blood-borne-virus-services.pdf.
62. Vojt G, Elliott L, Family H, et al. Post-treatment life-trajectories among people who inject drugs who completed hepatitis C treatment with direct acting antivirals: A thematic analysis. *British Journal of Health Psychology* 2025;30(3):e70005. doi: https://doi.org/10.1111/bjhp.70005
63. Samartsidis P, Martin NN, De Gruttola V, et al. Evaluating the power of the causal impact method in observational studies of HCV treatment as prevention. *Stat Commun Infect Dis* 2021;13(1):20200005. doi: 10.1515/scid-2020-0005 [published Online First: 20211011]
64. Samartsidis P, Seaman SR, Montagna S, et al. A Bayesian multivariate factor analysis model for evaluating an intervention by using observational time series data on multiple outcomes. *J R Stat Soc Ser A Stat Soc* 2021;28(1):155-66. doi: 10.1111/rssa.12569
65. Jugnarain DV, Halford R, Smith S, et al. Role of peer support in a hepatitis C elimination programme. *Journal of viral hepatitis* 2022;29(1):43-51. doi: 10.1111/jvh.13626 [published Online First: 20211027]
66. !!! INVALID CITATION !!! 42
67. Myring G, Lim AG, Hollingworth W, et al. Cost-effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for hepatitis C in patients receiving opioid substitution therapy: An economic evaluation alongside a pragmatic cluster randomised

trial. *J Infect* 2022;85(6):676-82. doi: 10.1016/j.jinf.2022.09.021 [published Online First: 20220925]
68. Radley A, de Bruin M, Inglis SK, et al. Clinical effectiveness of pharmacist-led versus conventionally delivered antiviral treatment for hepatitis C virus in patients receiving opioid substitution therapy: a pragmatic, cluster-randomised trial. *Lancet Gastroenterol Hepatol* 2020;5(9):809-18. doi: 10.1016/S2468-1253(20)30120-5 [published Online First: 2020/06/12]
69. Gliddon HD, Ward Z, Heinsbroek E, et al. Has the HCV cascade of care changed among people who inject drugs in England since the introduction of direct-acting antivirals? *Int J Drug Policy* 2024:104324. doi: 10.1016/j.drugpo.2024.104324 [published Online First: 20240112]
70. Simmons R, Ireland G, Irving W, et al. Establishing the cascade of care for hepatitis C in England-benchmarking to monitor impact of direct acting antivirals. *Journal of viral hepatitis* 2018;25(5):482-90. doi: 10.1111/jvh.12844 [published Online First: 2017/12/15]
71. McDonald SA, Palmateer N, McAuley A, et al. Estimating incidence rates of primary infection and reinfection with hepatitis C virus among people who inject drugs in Scotland: a model-based analysis of repeated cross-sectional survey data. *The Lancet Regional Health - Europe* 2026;60:101505. doi: https://doi.org/10.1016/j.lanepe.2025.101505
72. Mitchell HD, Clancy I, De Angelis D, et al. Using modelling and public health surveillance data to evidence progress towards the WHO incidence target for hepatitis C elimination in people who inject drugs - a review of complementary approaches in the United Kingdom. *International Journal of Drug Policy* 2025;146:105059. doi: https://doi.org/10.1016/j.drugpo.2025.105059
73. Murray E, Treweek S, Pope C, et al. Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. *BMC Med* 2010;8:63. doi: 10.1186/1741-7015-8-63 [published Online First: 20101020]