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Published in:
Addiction

DOI:
[10.1111/add.15459](https://doi.org/10.1111/add.15459)

Publication date:
2021

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

Palmateer, N. E., McAuley, A., Dillon, J. F., McDonald, S., Yeung, A., Smith, S., Barclay, S., Hayes, P., Shepherd, S. J., Gunson, R. N., Goldberg, D. J., Hickman, M., & Hutchinson, S. J. (2021). 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*, 116(10), 2893-2907. <https://doi.org/10.1111/add.15459>

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REDUCTION IN THE POPULATION PREVALENCE OF HCV VIRAEMIA AMONG PEOPLE WHO INJECT DRUGS ASSOCIATED WITH SCALE-UP OF DIRECT-ACTING ANTIVIRAL THERAPY IN COMMUNITY DRUG SERVICES: REAL WORLD DATA

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Running head: HCV among people who inject drugs

Declarations of competing interests

SJH has received honoraria from Gilead, outside of the submitted work. JFD declares research grants, in part supporting the scale-up of HCV treatment in Tayside, from AbbVie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharpe & Dohme, and Roche and other research grants and honoraria for lectures from AbbVie, Abbott, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharpe & Dohme and Roche, outside of the submitted work. PH has spoken or been on advisory boards for AbbVie, BMS, Eisai Ltd, Falk, Ferring, Gilead, Gore, Janssen, Lundbeck, MSD, Norgine, Novartis, ONO Pharmaceuticals, Pfizer and Roche. All other authors declare no competing interests.

Manuscript word count: 3,716

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/add.15459

ABSTRACT

Background and aims: There has been little empirical evidence to show the ‘real world’ impact of scaling-up direct-acting antiviral (DAA) treatment among people who inject drugs (PWID) on hepatitis C virus (HCV) viraemia at a population level. We aimed to assess the population impact of rapid DAA scale-up to PWID delivered through community services – including drug treatment, pharmacies, needle exchanges, and prisons – in the Tayside region of Scotland, compared with Greater Glasgow & Clyde (GGC) and the Rest of Scotland (RoS).

Design: Natural experiment, evaluated using data from national biennial surveys of PWID and national clinical data.

Setting: Services providing injecting equipment (2010-2018) and HCV treatment clinics (2017-2018) across Scotland.

Participants: 12,492 PWID who completed a questionnaire and provided a blood spot (tested for HCV-antibodies and RNA); 4,105 individuals who initiated HCV treatment.

Intervention and comparator: The intervention was rapid DAA scale-up among PWID, which occurred in Tayside. The comparator was GGC/RoS.

Measurements: Trends in HCV viraemia and uptake of HCV therapy over time; sustained viral response (SVR) rates to therapy by region and treatment setting

Findings: Uptake of HCV therapy (last year) among PWID between 2013-14 and 2017-18 increased from 15% to 43% in Tayside, 6% to 16% in GGC and 11% to 23% in RoS. Between 2010 and 2017-18, the prevalence of HCV viraemia (among antibody-positives) declined from 73% to 44% in Tayside, 67% to 58% in GGC and 64% to 55% in RoS. The decline in viraemia was greater in Tayside (2017-18 AOR 0.47, 95% CI 0.30-0.75, $p=0.001$) than elsewhere in Scotland (2017-18 AOR 0.89, 95% CI 0.74-1.07, $p=0.220$) relative to the baseline of 2013-14 in RoS (including GGC). Per-protocol SVR rates among PWID treated in community sites did not differ from those treated in hospital sites in Tayside (97.4% vs 100.0%, $p=0.099$).

Conclusions: Scale-up of direct-acting antiviral treatment among people who inject drugs can be achieved through hepatitis C virus (HCV) testing and treatment in community drug services whilst maintaining high sustained viral response rates and, in the Tayside region of Scotland, has led to a substantial reduction in chronic HCV in the population.

Word count: 331

INTRODUCTION

In many countries, people who inject drugs (PWID) comprise the largest population of people infected with hepatitis C virus (HCV) as well as the largest group at ongoing risk of infection.¹ In recognition of viral hepatitis as a global problem, the World Health Organization (WHO) has set targets to eliminate HCV, including a 80% reduction in HCV incidence by 2030.² To achieve this target, countries will need to provide optimal coverage of harm reduction services (including needle and syringe programmes and opioid agonist therapy), but will also need to prioritise major scale-up (i.e. expansion) of HCV treatment for PWID.³⁻⁶ Uptake of HCV therapy among PWID has been very limited until the recent introduction of direct-acting antiviral therapies (DAAs) – highly effective, tolerable and simple-to-administer therapies for the treatment of HCV infection.^{7,8,9} – Further, there has been little empirical evidence to show the ‘real world’ impact of scaling-up HCV DAA treatment among PWID on HCV viraemia at a population level.^{10,11,12}

In the Tayside region of Scotland, an evaluation of the impact of major and rapid scale-up of DAAs among PWID is underway, involving the provision of HCV testing and treatment across the full range of community services engaged with this population – including drug treatment, pharmacies, needle exchanges and prisons.¹³ The scale-up in Tayside, compared to other areas of Scotland, provides a unique opportunity to evaluate a natural experiment of the scale-up of DAAs on HCV viraemia prevalence in the PWID population.

Scotland is one of the few countries world-wide with comprehensive national surveillance systems, including large serial cross-sectional bio-behavioural surveys of PWID to monitor HCV infection and an HCV clinical database to monitor treatment outcomes.^{14,15} Using these data, we assess the early impact of DAA scale-up in Tayside, compared to other regions in Scotland. We aim to test the hypothesis that rapid scale-up of DAAs in community-based services translates into a decline in HCV viraemia among a population of PWID, and to test whether this rapid-scale up leads to any differences in sustained viral response (SVR) rates to therapy. Specifically, we examined: (i) the population-level prevalence of HCV therapy uptake, HCV viraemia and treatment-induced viral clearance among PWID over time and by region, (ii) the change in uptake of HCV therapy, HCV viraemia and treatment-induced viral clearance among PWID over time and by region, and (iii) SVR rates by region, treatment setting, and PWID status.

METHODS

The current study forms one component of the “Evaluating the population impact of hepatitis C direct acting antiviral treatment as prevention for people who inject drugs (EPIToPe)” study, a mixed methods evaluation of a natural experiment of HCV ‘Treatment as Prevention’ (TasP) among PWID.¹³ The ‘intervention’ consists of the scale-up of DAAs and expansion of care pathways in National Health Service (NHS) Tayside (an administrative health region in Scotland), with other sites in Scotland acting as the ‘controls’: NHS Greater Glasgow & Clyde (GGC) and the Rest of Scotland (RoS). NHS Tayside has an estimated 2,700 PWID, which compares to 10,000 and 17,300 in GGC and RoS, respectively.^{13,16,17} Prevalence of antibodies to HCV among PWID in Tayside in 2017-18 was 56%, as compared to 68% in GGC and 48% in RoS.¹⁴ The scale-up in Tayside involves the treatment of at least 500 PWID over a 2-3 year period beginning in 2017; mathematical modelling has indicated that this has the potential to reduce the chronic HCV prevalence among PWID in Tayside from approximately

30% to 10% or less. In the rest of Scotland, financial considerations precluded rapid scale-up of treatment beyond those eligible via the fibrosis-based prioritisation in place at the time.

The data analysed here relate to a time-point midway through scale-up, when approximately 200 PWID (i.e. 40% of the target) had been treated in community settings in Tayside. This study therefore evaluates the *early* impact of the DAA scale-up in Tayside. To address the aims described in the introduction, two sources of data were utilised, which are described further below and summarised in Box 1.

Data sources

Needle Exchange Surveillance Initiative (NESI)

NESI is a national bio-behavioural survey of PWID that has been undertaken approximately biennially since 2008-09 and covers an estimated 10-15% of the active PWID population in Scotland.¹⁴ Recruitment takes place at sites that provide sterile injecting equipment across Scotland (some of which may also provide opioid agonist therapy); sites are chosen to be broadly geographically representative and roughly 100 sites are included per sweep, representing approximately 50% of all sites that provide injecting equipment in Scotland. Trained interviewers facilitate the completion of a questionnaire and take a blood spot sample from all consenting participants. Dried blood spots (DBS) are tested for antibodies to HCV and HCV RNA; methods have been described in detail previously.^{14,18} Written informed consent was obtained from each patient included in the study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in approval by the West of Scotland Research Ethics Committee (reference 08/S0709/46).

As part of EPIToPe, approximately 200 PWID had been treated in community settings in Tayside during 2017. As part of the NESI 2017-18 sweep, interviews in Tayside were carried out in early 2018. Thus, four sweeps of NESI (2010, 2011-12, 2013-14 and 2015-16) were undertaken prior to, and one (2017-18) following, the early scale-up of DAAs.

Clinical database

The national Hepatitis C Clinical Database records clinical and epidemiological information on patients attending a specialist clinic for management of HCV infection and covers 17 out of the 18

Box 1. Summary of data sources

	Data source	
	Needle Exchange Surveillance Initiative (NESI)	Hepatitis C Clinical database
Research aim addressed	(i) To determine the population-level prevalence of uptake of HCV therapy, HCV viraemia and treatment-induced clearance among PWID over time, comparing NHS Tayside with NHS GGC/RoS (ii) To examine the associations between region/year and uptake of HCV therapy, HCV viraemia and treatment-induced clearance among PWID.	To determine SVR rates by region, treatment setting, and PWID status.
Brief description	Serial cross-sectional bio-behavioural surveys of PWID recruited at sites that provide sterile injecting equipment across Scotland	National database holding information on patients attending 17 out of the 18 HCV treatment clinics in Scotland (includes hospital, prison and community settings)
Dates data collected	Survey sweeps undertaken in 2010, 2011-12, 2013-14, 2015-16, 2017-18	Jan 2017 – Dec 2018 (date of treatment commencement)
Measurements	<ul style="list-style-type: none"> • HCV viraemia (HCV antibody positive and HCV RNA positive based on DBS results) • HCV therapy (self-reported and only available for 2013-14 onwards) • Treatment-induced viral clearance (combination of DBS result and self-reported HCV therapy, therefore only available for 2013-14 onwards) 	<ul style="list-style-type: none"> • ITT and per-protocol SVR
Comparators	<ul style="list-style-type: none"> • Region: NHS Tayside vs. NHS GGC vs. RoS • Time: survey year 	<ul style="list-style-type: none"> • PWID status • Region: NHS Tayside vs. NHS GGC vs. RoS • Treatment setting: hospital vs. prison vs. community
Analyses	<p>(i) Proportions of respondents who reported ever/last year uptake of therapy, with HCV viraemia (imputed), and with treatment-induced viral clearance (imputed) by region and survey year</p> <p>(ii) Multi-level logistic regression to examine associations between region/survey year and uptake of therapy in the last year, HCV viraemia, and treatment-induced viral clearance</p>	Proportions of respondents who achieved SVR by PWID status, region and treatment setting.

DBS = dried blood spot; GGC = Greater Glasgow & Clyde; HCV = hepatitis C virus; ITT = intention-to-treat; NHS = National Health Service; PWID = people who inject drugs; RNA = ribonucleic acid; RoS = Rest of Scotland; SVR = sustained viral response

clinics in Scotland (consisting of clinics in hospitals, as well as nurse-led clinics in prisons and community settings).¹⁵ We extracted data (age, sex assigned at birth, injecting status, treatment dates, SVR achievement, treatment setting and clinic) on patients who commenced therapy between January 2017 and December 2018. Data were complete to 31st March 2019, so patients who

commenced treatment at the end of December 2018 had sufficient time to complete treatment and have a follow-up SVR test.

Measurements

NESI

Based on the results of DBS testing, participants were categorised as HCV antibody positive or negative. Antibody positives were further classified as viraemic (HCV antibody positive and HCV RNA positive) or cleared (HCV antibody positive and HCV RNA negative). In the latest three surveys (2013-14, 2015-16 and 2017-18), participants were asked if they had commenced drug therapy for their HCV infection ever or in the last year. Participants were further categorised into the groups indicated in Box 2 by combining their HCV infection status from their DBS test with their self-reported uptake of therapy. Those with cleared infection who reported receiving HCV therapy in the past (i.e. Group A in Box 2) were defined as having “treatment-induced viral clearance”.

In order to generate appropriate denominators for HCV therapy uptake, we created definitions of individuals who were ‘eligible for therapy’. The denominator for those who had ever received therapy consisted of those with viraemia (i.e. Groups B and D in Box 2) plus those who had cleared infection with evidence of therapy (i.e. Group A). The denominator for therapy uptake in the last year consisted of those with viraemia (i.e. Groups F and H in Box 2) plus those who had cleared infection with evidence of therapy in the last year (i.e. Group E).

Box 2. Classification of respondents into groups based on HCV antibody/RNA status combined with self-reported history of HCV therapy (ever and in the last year)

	HCV antibody positive & HCV RNA negative (Cleared infection)	HCV antibody positive & HCV RNA positive (Viraemic infection)
Reported ever receiving therapy for HCV	Cleared infection through therapy (Group A)	Viraemic (relating to either failed therapy or re-infection following therapy) (Group B)
Did not report ever receiving therapy for HCV*	Cleared infection spontaneously (Group C)	(Group D)
Reported receiving therapy for HCV in the last year	Cleared infection through recent therapy (Group E)	Viraemic (relating to either failed therapy or re-infection following recent therapy) (Group F)
Did not report receiving therapy for HCV in the last year*	Cleared infection spontaneously or cleared through therapy more than one year ago (Group G)	Viraemic (Group H)

*Includes those who said they had not received treatment, as well as those who were unaware of their HCV infection

Clinical database

A SVR was defined as testing PCR negative for HCV RNA at either 24 weeks (pre-2014) or 12 weeks (2014 onwards) following completion of therapy, according to clinical guidelines.¹⁹ The time period is

from the confirmed end of treatment (rather than the expected end of treatment) if a patient prematurely discontinues. Only patients who had a documented SVR at 24+ weeks (pre-2014) or 12+ weeks (2014 onwards) were considered to have a SVR. Intention-to-treat (ITT) SVR rates were calculated as the number of patients who achieved SVR as a proportion of the number of patients who commenced treatment. Per-protocol SVR rates were calculated as the number of patients achieving SVR as a proportion of the number of patients with an SVR outcome recorded (i.e. excluding unknown results).

Statistical analysis

To describe the NESI participants, initial analyses looked at demographic and behavioural variables, by survey year and region: categorical variables were expressed as numbers and percentages whereas continuous variables were presented as means or medians. To test for differences across surveys, chi-square tests were performed for categorical variables and Wilk's lambda was calculated for continuous variables.

The main statistical analyses undertaken are described below under headings that relate to the three aims described in the introduction.

Population-level prevalence of uptake of HCV therapy, HCV viraemia and treatment-induced viral clearance (NESI data)

First, multiple imputation by chained equations (MICE) was applied to the NESI data to impute missing HCV antibody and HCV RNA results.²⁰ Missing data was assumed to be missing at random (MAR). This assumption, while not testable, was deemed plausible as there was no reason to believe that there was any systematic relationship between the absence of HCV antibody or HCV RNA measurement and the missing value. Survey year, region and time since onset of injecting were used as predictors in the imputation model and twenty imputed datasets were generated. Sensitivity analyses were performed by comparing the results from MICE to results generated from complete case analyses.

Where survey years were presented separately, NESI respondents who had participated more than once within a given survey year were identified (on the basis of initials, sex assigned at birth, date of birth, and NHS Board of recruitment) and only their first interview/DBS was included in the analysis. (When pooling data across the surveys, participants who had participated multiple times across survey years were considered – see multilevel logistic regression).

The proportions of respondents in NESI who reported ever/last year uptake of therapy, with viraemia, and with treatment-induced clearance were compared across survey sweeps and NHS Board regions (Tayside/GGC/RoS). GGC was presented separately because it is the largest NHS board in Scotland (representing approximately 33% of individuals with problem drug use in Scotland and 40% of all NESI respondents in the included survey years).¹⁷

Additionally, the setting where HCV therapy was initiated among respondents in the 2017-18 survey was examined and a chi-square test was performed to test for a difference in the proportion reporting community-initiated therapy by region.

Associations of region and survey year with uptake of HCV therapy, HCV viraemia and treatment-induced viral clearance (NESI data)

We used logistic regression to examine the association between the main predictors region and survey year and the outcomes uptake of therapy (in the last year), HCV viraemia (among antibody positives) and treatment-induced viral clearance (among antibody positives) in the NESI data collected from 2013-14 through 2017-18 (the models were restricted to these years because these were the only surveys in which the HCV treatment questions were asked). GGC was combined with RoS in these analyses to simplify the analysis of interactions between region and year. Univariable models were constructed for each predictor and outcome, followed by multivariable models adjusted also for sex (assigned at birth), age, time since onset of injecting, homelessness in the last six months (yes/no), receipt of methadone in the last six months (yes/no) and imprisonment in the last year (yes/no). Multivariable models were fitted with interactions between survey year and region and a likelihood ratio test (LRT) was conducted to test for evidence of the interaction. A multi-level regression modelling was used to take clustering and non-independence of observations among individuals into account, given some individuals had participated more than once across the surveys (identified on the basis of initials, sex (assigned at birth), date of birth, and NHS Board of recruitment).

SVR rates by region, treatment setting, and PWID status (clinical database)

Where individuals had multiple courses of treatment, the SVR relating to the treatment episode with the most recent completion date was used in the analysis. ITT and per-protocol SVR rates were calculated by PWID status, region (Tayside/GGC/RoS), and treatment setting (hospital/prison/community).

Analyses were undertaken in Stata version 13.1.²¹ Graphs were produced in Excel 2016 and R version 3.5.1.^{22,23}

The analysis was not pre-registered on a publicly available platform and therefore the results should be considered exploratory.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication.

RESULTS

A total of 12,492 PWID who participated in the NESI survey and 4,105 individuals who initiated HCV treatment were included in this study. A further breakdown of the sample sizes that were included in the different analyses is given in Figures 1a and 1b. An overview of the NESI samples recruited in Tayside, GGC, and RoS are presented in supplementary tables S1-S3, respectively. The prevalence of HCV antibodies in Tayside (n=818), GGC (n=5,105), and RoS (n=6,358) ranged between 41-56%, 63-69% and 44-52%, respectively, between 2010 and 2017-18. Approximately 70-80% of the sample were male, and this was consistent across the surveys and regions. Average age and time since onset of injecting increased across the surveys in all regions, suggestive of an ageing cohort effect. Excessive alcohol consumption was generally lower in Tayside compared with GGC and RoS (ranging

from 10-19%, 23-30% and 19-30%, respectively). Cocaine injection in the last six months was also generally lower in Tayside and showed evidence of an increase across the surveys in all regions (from 4% to 14% in Tayside, from 16% to 50% in GGC, and from 7% to 19% in RoS).

Population-level prevalence of uptake of HCV therapy, HCV viraemia and treatment-induced viral clearance (NESI data)

In Scotland overall, the proportion of those who said they had ever received therapy or received therapy in the last year increased from 19% (167/863) and 9% (72/800) in 2013-14 to 38% (301/785) and 21% (144/680) respectively in 2017-18 (Table 1). In Tayside, uptake of therapy in the last year increased from 15% (12/81) to 43% (26/61) between 2013-14 and 2017-18, as compared with 6% (22/378) to 16% (50/322) in GGC and 11% (38/341) to 23% (68/297) in RoS.

Sensitivity analyses comparing the results from data imputation to results generated from complete case analyses are presented in supplementary table S4. Results were robust to these changes. Between 2010 and 2017-18, the prevalence of HCV viraemia in Tayside decreased from 30% (95% CI 24-36%) in 2010 to 24% (95% CI 18-30%) in 2017-18 among all respondents and from 73% (95% CI 64-82%) to 44% (95% CI 34-55%) among antibody positives (Table 1 and Figure 2). The latter compares to declines from 67% (95% CI 64-70%) to 58% (95% CI 54-63%) and 64% (95% CI 61-68%) to 55% (95% CI 50-59%) among antibody-positives in GGC and RoS, respectively.

The prevalence of treatment-induced clearance (among antibody positives) increased in Tayside from 16% (95% CI 9-23%) to 40% (95% CI 30-49%), in comparison to 5% (95% CI 3-6%) to 14% (95% CI 11-17%) in GGC and 10% (95% CI 8-13%) to 22% (18-25%) in RoS.

Figure 3 displays the setting where HCV therapy was initiated among respondents in the 2017-18 survey. A much larger proportion of respondents (74%, 62/84) in Tayside reported starting treatment in the community, as compared with GGC (11%, 15/137) and RoS (27%, 52/190) ($\chi^2=108.86$, $p<0.001$).

Associations of region and survey year with uptake of HCV therapy, HCV viraemia and treatment-induced viral clearance (NESI data)

PWID recruited in Tayside were more likely to have reported uptake of therapy, after adjustment for survey year and other variables (Table S5: adjusted odds ratio [AOR] 3.13, 95% CI 2.22-4.41). While there was insufficient evidence for an interaction between year and region (likelihood ratio test/LRT $p=0.112$), stratified analyses were suggestive of a larger increase in uptake of therapy in Tayside (AOR 5.19, 95% CI 2.87-9.37) as compared with RoS (AOR 2.35, 95% CI 1.67-3.31), where the baseline for comparison was 2013-14 RoS (Table 2).

After adjustment, respondents in Tayside had lower odds of viraemia (AOR 0.66, 95% CI 0.52-0.84) as compared with those in the rest of Scotland, with evidence of an interaction between region and year (LRT $p=0.034$), indicating that there was a larger reduction in HCV viraemia in Tayside (AOR 0.47, 95% CI 0.30-0.75) as compared with RoS (AOR 0.89, 95% CI 0.74-1.07), when compared to RoS 2013-14 (Tables 2 and S5).

After adjustment, respondents in Tayside were more likely to have treatment-induced clearance (Table S5: AOR 3.57, 95% CI 2.65-4.81) as compared with those in the rest of Scotland. There was

insufficient evidence of an interaction between region and year (LRT $p=0.254$) but some evidence of a larger increase in treatment-induced clearance in Tayside (AOR 4.12, 95% CI 2.56-6.61) as compared with RoS (AOR 2.49, 95% CI 1.88-3.30) (Table 2).

SVR rates by region, treatment setting, and PWID status (clinical database)

There was a difference of approximately 6 to 8 percentage points in ITT rates between PWID and non-PWID in GGC (74% vs 81%, $p=0.007$), RoS (66% vs. 72%, $p=0.008$) and Tayside (78% vs. 86%, $p=0.119$) (Table 3, Figure 4, Figure S1). In all Scottish regions, per-protocol SVR rates did not differ significantly between PWID and non-PWID. There was evidence that ITT SVR rates were lower in community settings as compared with hospital settings in GGC (70% vs. 80%, $p<0.001$), RoS (65% vs. 72%, $p=0.01$) and Tayside (78% vs. 85%, $p=0.121$). Per-protocol SVR rates did not differ significantly across treatment settings in any Scottish regions.

DISCUSSION

In this study, we found that rapid scale-up of DAAs among PWID in community settings in Tayside led to a greater decline in the prevalence of viraemic infection among PWID than elsewhere in Scotland. There was also evidence that HCV viraemia declined, to a lesser extent, in other sites in Scotland correlated with increases in HCV treatment. Further, we found that the increase in community treatment in Tayside was not associated with any reduction in SVR rates in per-protocol analyses.

While numerous mathematical modelling studies have examined the hypothetical impact of scaling up HCV therapy on chronic HCV prevalence, there has been little empirical evidence to corroborate these models.¹¹⁻¹³ One study has examined the impact of DAAs on chronic HCV prevalence at a sub-national level (in prisons).²⁴ Other “real world” evidence published focuses on scaling up treatment and SVR, rather than impact at a population level.²⁵⁻²⁷ To our knowledge, only one other study to date has used national data to examine the impact of treatment scale-up among PWID on viraemic prevalence at a population level. They found that treatment uptake (ever) among Australian PWID increased from 10% to 41%, and that viraemic prevalence decreased from 43% to 25% overall, between 2015 and 2017.¹⁰ However, direct comparisons with Australia cannot be drawn, given the different interventions: they evaluated the impact (pre vs. post) of the introduction of completely unrestricted access to DAAs across the country, whereas we evaluated an intervention (that had been demonstrated in mathematical models to deliver population-level change in HCV viraemia) involving scale-up of DAAs in a specific PWID population, compared with a natural control group, through delivery of therapy across multiple community-based settings. Further, a limitation recognised in the Australian study was the amount of missing RNA results from DBS testing (44%-60% of antibody positive samples across the three years of data), which may have led to bias within their analysis, compared in our study to 4%-11% missing RNA results.

It is notable treatment interventions had been occurring in Tayside prior to EPIToPe, albeit to a much lesser extent, with approximately 100 PWID treated with interferon-based therapies during 2012-2016.²⁸ These treatment interventions may account for the higher uptake of therapy at ‘baseline’ (i.e. pre-EPIToPe scale-up) in Tayside as compared with other regions. However, while these early interventions did not constitute ‘rapid’ scale-up, they can nevertheless be considered as part of the package of treatment interventions delivered to PWID in Tayside and their impact can be seen pre-

2017-18. We have demonstrated the impact of partial scale-up; future sweeps of NESI will allow us to measure further progress towards reducing viraemia to 10% or lower.

DAA scale-up is one of the key tools for countries to achieve HCV elimination. In their strategy for elimination of viral hepatitis, the WHO have set targets relating to incidence of HCV infection, but not for prevalence viraemia/chronic infection.² We believe that monitoring impact on prevalence of viraemia is a necessity to evaluate the direct, short-term impact of DAA scale-up as any increase in recent therapy uptake would be directly observable in viraemic prevalence. We acknowledge that is nevertheless important, in the longer term, to monitor incidence, as this can also impact on viraemic prevalence. In particular, incidence of HCV reinfection is a key consideration with regard to HCV elimination among PWID: if population-level viremia is not rapidly reduced to sufficiently low levels, then reinfections will cause a rise in the HCV viraemic prevalence.²⁹ Future analyses examining the impact of full scale-up in Tayside will consider both primary incident infections and re-infections.

We have also provided evidence that rapidly scaling up treatment to people through community drug services (and who are therefore likely continuing to inject either during and/or after therapy) does not compromise SVR rates. Though the intention-to-treat SVR rates were lower in community sites (as compared with hospital) and among PWID, this is likely a result of PWID not attending their appointment for confirmation of SVR and is therefore a reflection of lack of follow-up rather than lack of SVR attainment.³⁰ The latter is corroborated by NESI data from Tayside in 2017-18, which show that, of those who said they had been initiated on treatment in the last year (who we can assume are a mixture of individuals who did/did not return for a confirmatory SVR test), 96% were PCR negative (95% CI 81-99%). Non-compliance is nevertheless a concern, as there is evidence to suggest poor health outcomes among non-compliant individuals; however, they represent a small minority of the patients that commence therapy.³¹ Although the DAAs are highly tolerable, easy to take/administer and involve a much shorter course of treatment than the interferon-based therapies, compliance can nevertheless be challenging for individuals with complex personal and social circumstances.³⁰

A major strength of our analysis is the “natural experiment” design, whereby Tayside represents the “intervention” group and GGC/RoS are the “control” group. A further strength of our study is the data sources, which are comprehensive and national: few countries are in a position to be able to measure population-level changes in HCV viraemia among PWID, NESI being one of only four serial bio-behavioural studies of its kind internationally.^{10,32,33} However, we acknowledge several limitations. First, we relied on self-report for uptake of HCV therapy, which may be subject to recall and social desirability biases. Second, there is sampling variation between the serial surveys and could be a potential reason for differences between the survey sweeps. However, most sample characteristics were relatively stable across the period examined or followed expected trends - such as the increase in cocaine injecting.³⁴ Third, there were variations in prevalence of HCV antibody in Tayside, which was 41%-42% in 2010-2012 and increased to 56% in 2013-14. These changes may result from selection bias because, as part of the intervention, treatment became available at some of the needle exchange and drug treatment settings where NESI recruitment takes place, potentially attracting more hepatitis C infected clientele, thereby artificially increasing the prevalence.^{28,35} To account for this issue, we analysed and presented the viraemia data among HCV antibody positives, which removes any variation in overall antibody prevalence (we have also presented the prevalence of viraemia among all respondents for comparison purposes). We acknowledge that this selection

bias could also have affected the rates of treatment uptake and viraemia itself for the same reasons. However, if we examine the distribution of settings where individuals initiated treatment from the clinical database (which captures a comprehensive picture of all those receiving treatment), 24%, 9% and 67% of treatment initiations in Tayside in 2017/2018 occurred in hospitals, prisons and community settings, respectively. Comparing that to the distribution obtained from NESI respondents recruited in Tayside shows that the oversampling from community settings, while not insignificant, is not vast (with 11%, 10% and 79% of treatment initiations in 2017-18 in hospitals, prisons and community settings, respectively). A fourth limitation of the study relates to the assays used to detect HCV antibody and RNA on DBS. The sensitivity and specificity of the antibody test are 99% and 100%, respectively; the corresponding values for the PCR test are 100% and 96%.^{36,37} There is therefore a very small chance of false negatives or false positives on both tests. We may have missed individuals who had very recently been infected given that antibody and RNA levels may fall below the lower limits of detection during this time.³⁸ However, these are likely to be very small numbers and should therefore not affect our viraemic prevalence estimates.¹⁸ Finally, the incomplete treatment data was a limitation and is reflected in the ITT SVR rates as they include missing confirmatory tests.

In conclusion, we have demonstrated the feasibility and effectiveness of an approach that involves HCV testing and treatment in a range of community services engaged with PWID, in increasing HCV treatment uptake and thereby reducing the prevalence of HCV viraemia. Our findings provide compelling evidence for other countries to plan their HCV elimination strategies.

Acknowledgments

We would like to acknowledge the NIHR Health Protection Research Unit in Behavioural Science and Evaluation, HCV specialist nurses and HCV treatment centres, the NESI Steering Group, the HCV Prevention Leads Group, NESI researchers, staff from the West of Scotland Specialist Virology Centre, Avril Taylor for her role in the conception of the NESI study, and the respondents who volunteered their time to participate in the NESI studies.

Financial support

This study was funded by Public Health Scotland (PHS) and the National Institute for Health Research (NIHR). NIHR funding was through the Programme Grants for Applied Research programme (Grant Reference Number RP-PG-0616-20008). Research grants from AbbVie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharpe & Dohme, and Roche supported, in part, the scale-up of HCV treatment in Tayside.

Author contributions

SJH and DJG conceived and designed the NESI study. SJH, AMc and NEP implemented the NESI study. SJS and RNG analysed the dried blood spot samples for the NESI study. PH, JFD, SJH and DJG conceived and developed the Scottish HCV Clinical database. SJH and DJG oversee, and SS coordinates, the collation of local clinical data to form national surveillance of HCV treatment in Scotland; while JFD, SB, and PH contribute local data to the Scottish HCV Clinical database. MH, SJH, JFD and DJG conceived and designed the EPIToPe study. JFD lead on the development of services to scale-up HCV treatment in NHS Tayside. MH, SJH and NEP contributed to conception of the statistical

analysis. NEP, AMc, SMc, AY and SS contributed to the data analysis and generation of result tables and figures. All authors interpreted the findings. NEP drafted the manuscript and all remaining authors contributed to critical review and development of the final manuscript.

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Table 1. Trends in uptake of HCV therapy and estimated prevalence of HCV viraemia and treatment-induced viral clearance among people who inject drugs attending injection equipment provision services across Scotland, 2010-2018 (data from the Needle Exchange Surveillance Initiative/NESI)

		Region	Survey sweep				
			2010	2011-12	2013-14	2015-16	2017-18
Therapy uptake*	Ever	All Scotland	N/A	N/A	19% (167/863)	17% (171/1006)	38% (301/785)
		Tayside	N/A	N/A	31% (28/90)	35% (31/89)	65% (49/75)
		GGC	N/A	N/A	14% (54/399)	14% (57/422)	31% (111/360)
		Rest of Scotland	N/A	N/A	23% (85/374)	17% (83/495)	40% (141/350)
	Last year	All Scotland	N/A	N/A	9% (72/800)	7% (66/949)	21% (144/680)
		Tayside	N/A	N/A	15% (12/81)	23% (18/79)	43% (26/61)
		GGC	N/A	N/A	6% (22/378)	3% (13/406)	16% (50/322)
		Rest of Scotland	N/A	N/A	11% (38/341)	8% (35/464)	23% (68/297)
Prevalence of HCV viraemia**	All	All Scotland	37% (35%-39%)	33% (31%-35%)	35% (33%-37%)	38% (36%-40%)	32% (29%-34%)
		Tayside	30% (24%-36%)	24% (16%-32%)	34% (27%-40%)	32% (26%-38%)	24% (18%-30%)
		GGC	45% (42%-47%)	39% (36%-43%)	45% (41%-48%)	47% (43%-50%)	40% (36%-43%)
		Rest of Scotland	31% (28%-33%)	28% (25%-31%)	27% (25%-30%)	34% (31%-36%)	27% (24%-29%)
	HCV antibody positives	All Scotland	66% (64%-68%)	61% (58%-64%)	60% (57%-63%)	67% (64%-69%)	55% (52%-58%)
		Tayside	73% (64%-82%)	59% (45%-73%)	60% (51%-69%)	58% (48%-67%)	44% (34%-55%)
		GGC	67% (64%-70%)	62% (58%-67%)	64% (60%-68%)	72% (68%-76%)	58% (54%-63%)
		Rest of Scotland	64% (61%-68%)	61% (56%-65%)	57% (53%-61%)	65% (61%-68%)	55% (50%-59%)
Prevalence of treatment-induced viral clearance**	All	All Scotland	N/A	N/A	5% (4%-6%)	4% (3%-5%)	11% (10%-13%)
		Tayside	N/A	N/A	9% (5%-13%)	10% (6%-14%)	22% (16%-27%)
		GGC	N/A	N/A	3% (2%-4%)	3% (2%-4%)	10% (8%-12%)
		Rest of Scotland	N/A	N/A	5% (4%-6%)	4% (3%-5%)	10% (9%-12%)
	HCV antibody positives	All Scotland	N/A	N/A	8% (7%-10%)	7% (6%-8%)	20% (18%-22%)
		Tayside	N/A	N/A	16% (9%-23%)	18% (12%-25%)	40% (30%-49%)
		GGC	N/A	N/A	5% (3%-6%)	4% (3%-6%)	14% (11%-17%)
		Rest of Scotland	N/A	N/A	10% (8%-13%)	7% (5%-9%)	22% (18%-25%)

GGC = Greater Glasgow & Clyde; HCV = hepatitis C virus; N/A = not applicable

*among therapy-eligible respondents; see methods for definitions

**Missing antibody and RNA data have been imputed; see methods.

Table 2. Logistic regression analyses of a) uptake of therapy in the last year, b) HCV viraemia (among HCV antibody positives) and c) treatment-induced viral clearance (among HCV antibody positives), by region and survey year, among people who inject drugs attending injection equipment provision services across Scotland, 2013-2018* (data from the Needle Exchange Surveillance Initiative/NESI)

Outcome	Predictor		AORs*	
			AOR (95% CI)	p-value
Uptake of therapy (in last year)†	Rest of Scotland (including GGC)	2013-14	(n=2,680) 1	
		2015-16	0.65 (0.44-0.97)	0.033
		2017-18	2.35 (1.67-3.31)	<0.001
	Tayside	2013-14	2.12 (1.10-4.08)	0.025
		2015-16	2.87 (1.67-4.92)	<0.001
		2017-18	5.19 (2.87-9.37)	<0.001
HCV viraemia (among HCV antibody positives)	Rest of Scotland (including GGC)	2013-14	(n=3,681) 1	
		2015-16	1.50 (1.27-1.77)	<0.001
		2017-18	0.89 (0.74-1.07)	0.220
	Tayside	2013-14	0.96 (0.64-1.44)	0.853
		2015-16	0.57 (0.38-0.84)	0.005
		2017-18	0.47 (0.30-0.75)	0.001
Treatment-induced viral clearance (among HCV antibody positives)	Rest of Scotland (including GGC)	2013-14	(n=3,681) 1	
		2015-16	0.70 (0.51-0.96)	0.027
		2017-18	2.49 (1.88-3.30)	<0.001
	Tayside	2013-14	2.46 (1.40-4.33)	0.002
		2015-16	4.37 (2.60-7.35)	<0.001
		2017-18	4.12 (2.56-6.61)	<0.001

AOR = adjusted odds ratio; CI = confidence interval; HCV = hepatitis C virus; GGC = Greater Glasgow & Clyde

*AORs derived from multivariable models with interaction effects (see Table S5 for univariable and main effects models). Multivariable models are also adjusted for sex, age, time since onset of injecting, homelessness (last six months), receipt of methadone (last six months) and imprisonment (last year)

†among therapy-eligible respondents; see methods for definitions

Table 3. Intention-to-treat/per-protocol SVR rates by region, PWID status and treatment setting among patients initiated on HCV therapy in Scotland during 2017-2018 (data from the Hepatitis C Clinical Database)

	Region	PWID*		Non-PWID*		X ² , p-value		
		n/N	% (95% CI)	n/N	% (95% CI)			
Intention-to-treat	All Scotland	2227/3111	71.6% (70.0%-73.2%)	765/994	77.0% (74.2%-79.5%)	11.021, p=0.001		
	Tayside	343/441	77.8% (73.6%-81.6%)	61/71	85.9% (75.6%-93.0%)	2.433, p=0.119		
	GGC	1099/1477	74.4% (72.1%-76.6%)	345/427	80.8% (76.7%-84.4%)	7.379, p=0.007		
	Rest of Scotland	785/1193	65.8% (63.0%-68.5%)	359/496	72.4% (68.2%-76.3%)	6.937, p=0.008		
Per-protocol	All Scotland	2227/2267	98.2% (97.6%-98.7%)	765/777	98.5% (97.3%-99.2%)	0.167, p=0.683		
	Tayside	343/351	97.7% (95.6%-99.0%)	61/61	100% (94.1%-100%)	1.418, p=0.234		
	GGC	1099/1112	98.8% (98.0%-99.4%)	345/352	98.0% (96.0%-99.20%)	1.333, p=0.248		
	Rest of Scotland	785/804	97.6% (96.3%-98.6%)	359/364	98.6% (96.8%-99.6%)	1.219, p=0.270		
	Region	Hospital		Prison		Community**		X ² , p-value (comparing community vs. hospital)
		n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	
Intention-to-treat	All Scotland	1923/2507	76.7% (75.0%-78.3%)	207/349	59.3% (54.0%-64.5%)	841/1194	70.4% (67.8%-73.0%)	16.815, p<0.001
	Tayside	104/123	84.6% (76.9%-90.4%)	34/38	70.8% (55.9%-83.1%)	266/341	78.0% (73.2%-82.3%)	2.398, p=0.121
	GGC	1038/1297	80.0% (77.8%-82.2%)	84/144	58.3% (49.8%-66.5%)	322/463	69.6% (65.1%-73.7%)	21.356, p<0.001
	Rest of Scotland	781/1087	71.9% (69.1%-74.5%)	89/157	56.7% (58.6%-64.6%)	253/390	64.9% (59.9%-69.6%)	6.655, p=0.010
Per-protocol	All Scotland	1923/1957	98.3% (97.6%-98.8%)	207/211	98.1% (95.2%-99.5%)	841/855	98.4% (97.3%-99.1%)	0.035, p=0.851
	Tayside	104/104	100.0% (96.5%-100.0%)	34/35	97.1% (85.1%-99.9%)	266/273	97.4% (94.8%-99.0%)	2.717, p=0.099
	GGC	1038/1054	98.5% (97.6%-99.1%)	84/87	96.6% (90.3%-99.3%)	322/323	99.7% (98.3%-100.0%)	2.961, p=0.085
	Rest of Scotland	781/799	97.8% (96.5%-98.7%)	89/89	100.0% (95.9%-100.0%)	253/259	97.7% (95.0%-99.2%)	0.004, p=0.952

CI = confidence interval; GGC = Greater Glasgow & Clyde; HCV = hepatitis C virus; PWID = people who inject drugs; SVR = sustained viral response

*Patient had indicated ever injecting drugs

**Community sites include needle exchanges, pharmacies, drug treatment centres, and other outreach clinics

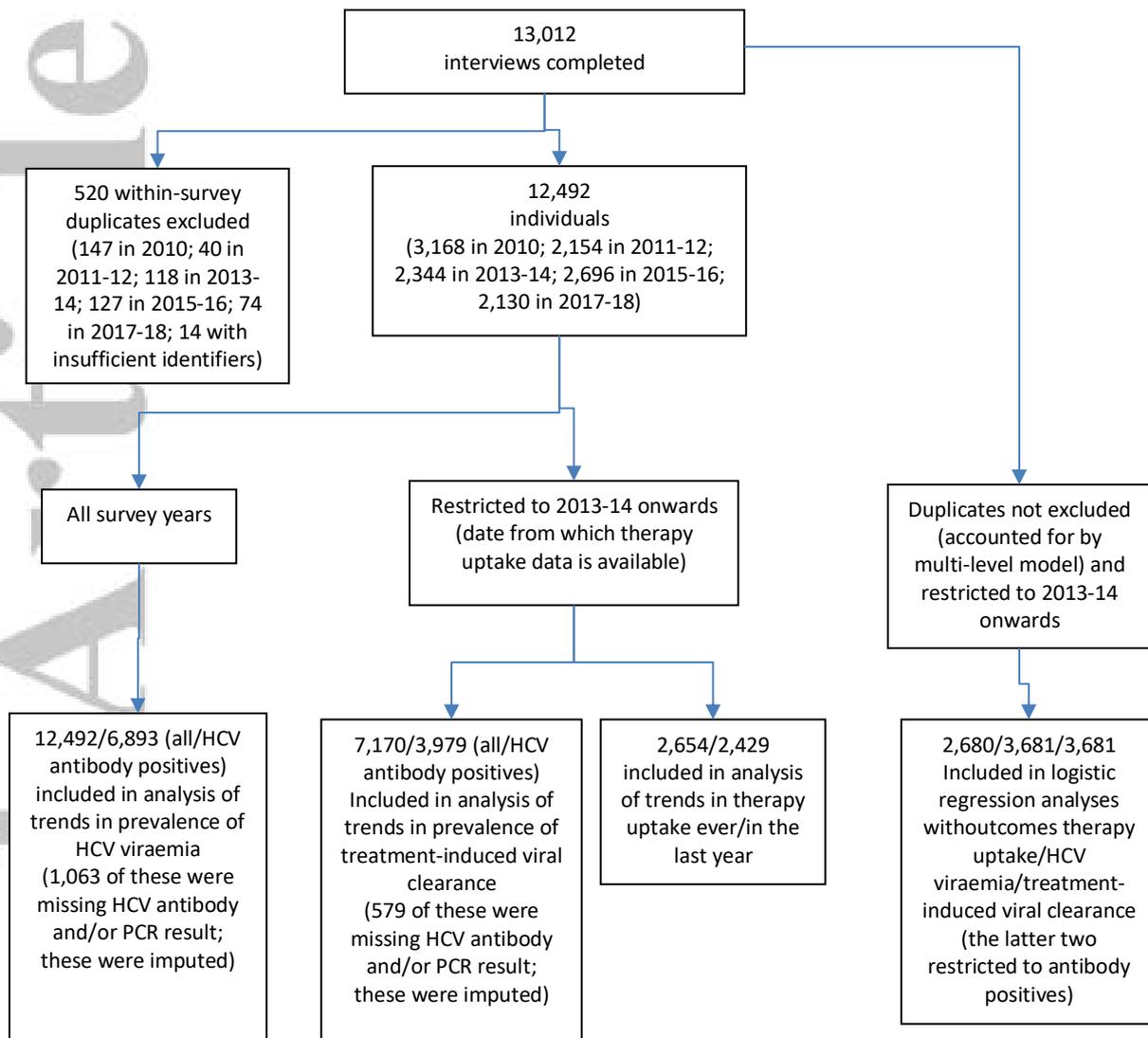


Figure 1a. Number of participants included in the analysis of population-level prevalence of uptake of HCV therapy, HCV viraemia and treatment-induced viral clearance and the analysis of associations of region and survey year with uptake of HCV therapy, HCV viraemia and treatment-induced viral clearance (data from the Needle Exchange Surveillance Initiative/NESI)

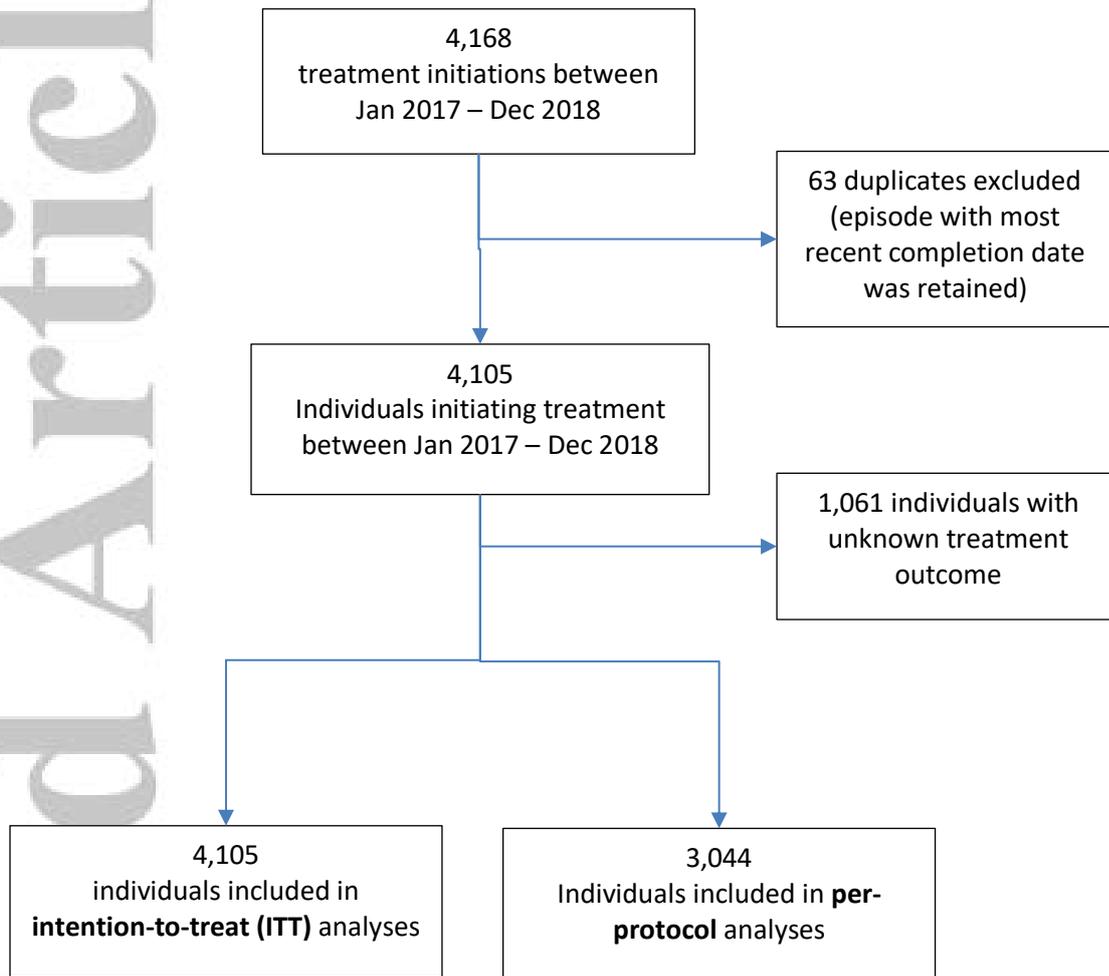


Figure 1b. Participants included in the analysis of SVR rates (data from the Scottish Hepatitis C Clinical Database).

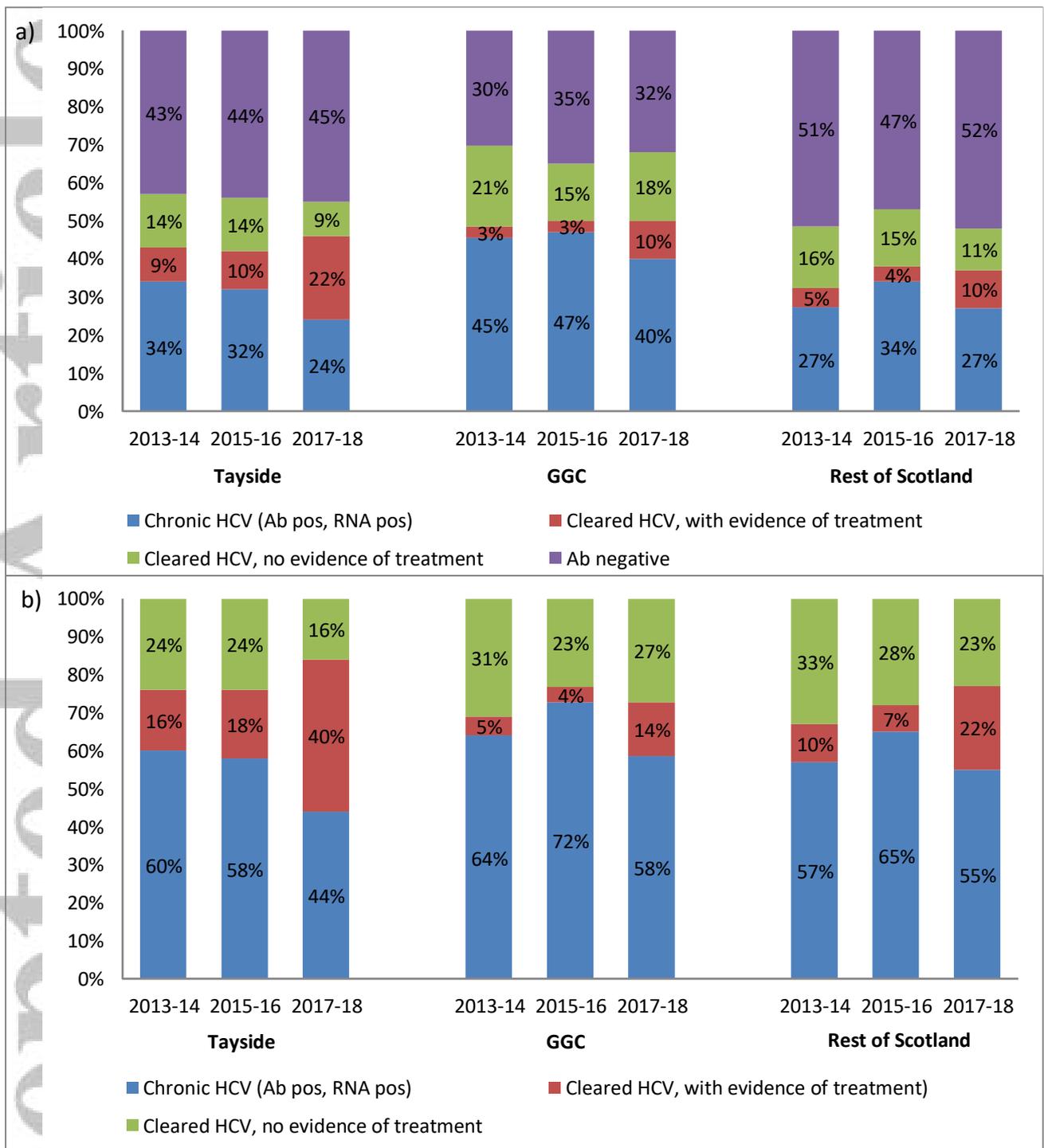


Figure 2. Prevalence of viraemic and cleared HCV infection among people who inject drugs attending injection equipment provision services across Scotland, 2013 to 2018. Figures present a) all respondents and b) HCV antibody positives only (data from the Needle Exchange Surveillance Initiative/NESI).

Ab = antibody; GGC = Greater Glasgow & Clyde; HCV = hepatitis C virus; RNA = ribonucleic acid

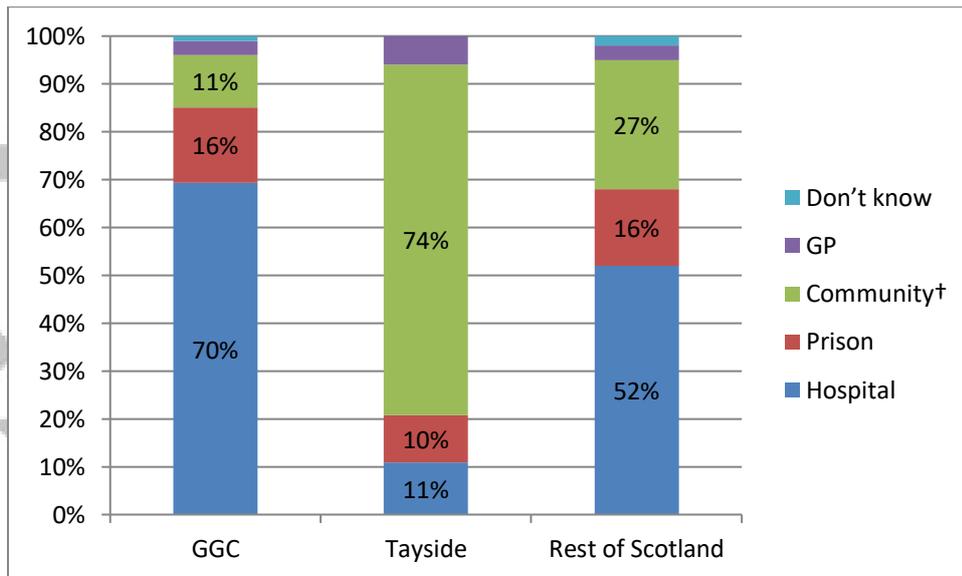


Figure 3. Site of initiation of most recent course of HCV therapy* among people who inject drugs attending injection equipment provision services across Scotland, 2017-18 (data from the Needle Exchange Surveillance Initiative/NESI).

GGC = Greater Glasgow & 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

Accepted

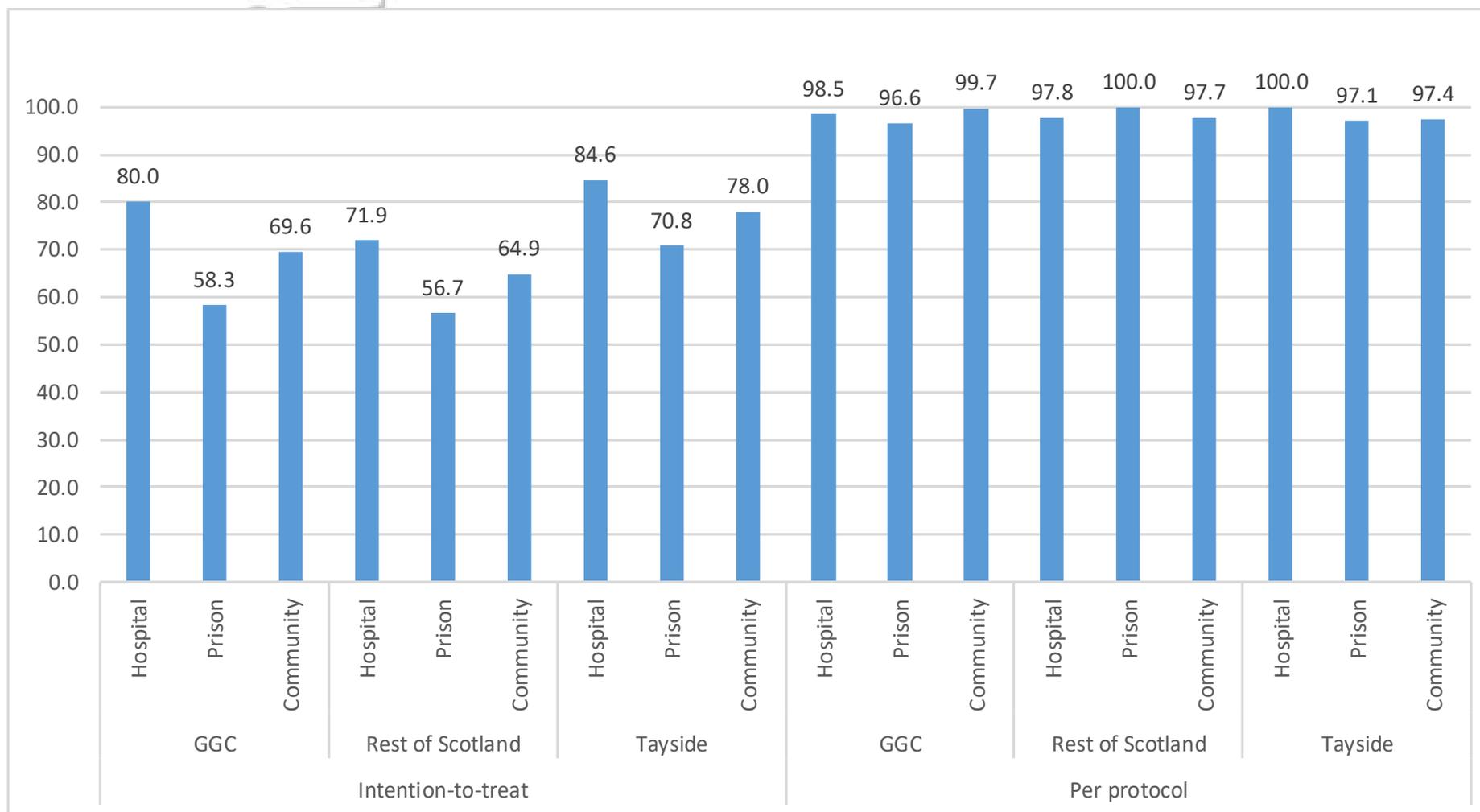


Figure 4. Intention-to-treat/per-protocol SVR rates by region and treatment setting among patients attending specialist liver clinics in Scotland, 2017-2018 (data from the Hepatitis C Clinical Database).

GGC = Greater Glasgow & Clyde; SVR = sustained viral response