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RESEARCH ARTICLE

Toward microelimination of hepatitis C and HIV coinfection in NHS Tayside, Scotland: Real-world outcomes

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Abstract

Background and aims: NHS Tayside is a health board in Scotland which serves around 400 000 residents. Approximately, 2761 are estimated to be persons who inject drugs (PWID), and therefore at risk of infections such as hepatitis C (HCV) and HIV. There are few studies exploring mechanisms and success of eliminating HCV in HIV co-infected PWID using real-world data. This study aims to empirically assess HCV treatment outcomes in people living with HIV (PLHIV) to evaluate progress toward microelimination of HCV in the HIV-positive population in Tayside.

Methods: HCV testing and treatment details for PLHIV stored on clinical databases dating from 2001 were extracted and anonymized. HCV treatment uptake among co-infected patients eligible for HCV treatment was calculated. Reinfection incidence was calculated in person years. Confidence intervals were calculated assuming Poisson distribution. Caldicott Guardian approval was obtained to access patient data (ref: IGTCAL 5677).

Results: Ninety-six percent of PLHIV were tested for HCV across nine services and aware of their HCV status. From 2001 to 2019, 58 PLHIV were HCV co-infected. Four left the area and five died prior to HCV treatment. Forty-nine were eligible for HCV treatment. Thirty were treated with PEGylated interferon (Peg-IFN); 18 with direct acting antivirals (DAA). One is yet to be treated. Twelve treated with Peg-IFN did not achieve sustained viral response (SVR12); 10 were retreated, two died prior to re-treatment. Injecting drug use was the mode of HCV transmission for 39 of 49 patients. Proportion who achieved SVR12 is 75%; 92% if treated with DAAs. Annual proportions of PLHIV treated for HCV increased from 3.57% in the Peg-IFN era to 66.67% in the DAA era. Reinfection incidence is 0.2 per 100 person years (CI −0.3 to 0.7).

Conclusions: NHS Tayside has made progress toward microelimination of HCV among PLHIV. The most common mode of HCV transmission in PLHIV in NHS Tayside is injecting drug use. DAAs increased the proportion of co-infected PLHIV treated for HCV and produced superior SVR12 results compared to Peg-IFN.

KEYWORDS

coinfection, drug users, elimination, hepatitis C, HIV, Injecting, microelimination, people Who Inject Drugs, PWID, Scotland; direct Acting Antivirals

1 | INTRODUCTION

The World Health Organization (WHO) estimates that approximately 37 million people are living with HIV (PLHIV) globally; of these, 2.9 million are co-infected with hepatitis C (HCV).[1] The WHO urges that efforts to effectively diagnose, treat, and link to care those people who are co-infected are prioritized.[2] In Scotland, of the estimated 4726 persons diagnosed with HIV, 565 (11.9%) have had a reactive HCV antibody (IgG) test,[3] indicating that they have been exposed to HCV. Approximately, 0.3% of the UK population[4] and 1% of the Scottish population have been infected with HCV[5]; this increases to 58% among people who inject drugs (PWID), the highest risk group for transmission of HCV in Scotland.[6]

HCV prevalence is proportionally higher in HIV-positive individuals, especially in PWID, than in HIV-negative individuals.[7] Increased risk of negative health outcomes associated with HCV for those co-infected with HIV, such as rapid acceleration of liver fibrosis,[8] increased risk of hepatocellular carcinoma,[9] and mortality,[10] over those mono-infected with HCV or HIV, suggests the co-infected subgroup is a treatment priority. The British HIV Association called for elimination of HCV in HIV patients by 2021.[11] Furthermore, *The Lancet: HIV* asserts that, "because HIV and HCV share transmission pathways, targeted elimination, is an obvious and welcome synergy."[12]

Using the WHO target of a 90% reduction in new chronic HCV infections, and a 65% reduction in liver-related deaths by 2030 as a guide,[1] this article investigates NHS Tayside's progress toward eliminating HCV among PLHIV. Data presented here only represents the HIV-diagnosed population living in the region, and any PLHIV who are/were unaware of their status are not included in the analyses. However, Scotland has made strong progress on the UNAIDS 90-90-90 targets[13] for PLHIV, with data indicating that 91% of PLHIV in Scotland know their HIV status, 98% are on ART, and 97% show evidence of viral suppression,[14] so the proportion of undiagnosed PLHIV in the region is likely to be low.

Tayside's population is relatively stable, and widely dispersed through a mixture of rural towns and villages, to larger towns and cities across approximately 3000 mile^2. The integrated care pathway for blood-borne viruses (BBV) has been developed to collocate HCV services where possible to overcome the barriers of population dispersion and geography. HCV testing and treatment, including for PLHIV, is available through community pharmacies, prison estates, substance misuse services, specialist clinics, general practice (family practice), and injecting equipment provision sites (Figure 1). The Health Board has been historically pro-active in testing and treating for HCV among PLHIV in the region, with the goal of "micro-eliminating"[15] HCV within this population becoming more realistic with the introduction of Direct Acting Antivirals (DAA) for HCV.

There are few studies exploring real-world mechanisms and success rates of eliminating HCV in the HIV co-infected population whose main risk factor is injecting drug use. Only one published study using DAAs to eliminate HCV in HCV-HIV co-infected patients included PWID.[16] An ongoing prospective study in Australia is also examining microelimination of HCV in a co-infected cohort of PWID.[17] Two other microelimination studies, one from the Netherlands,[18] and a Swiss treatment as prevention (TasP) study, examine HCV elimination among HCV- HIV co-infected men who have sex with men (MSM).[19]

This descriptive cohort study aims to empirically assess HCV testing and treatment outcomes for PLHIV in the NHS Tayside health board, in the east of Scotland, to measure progress toward microelimination of HCV among PLHIV in the region. The analyses are further intended to review local practice, and document the multi-stakeholder integrated care pathway for BBVs, which may be of interest to other regions considering a HCV microelimination strategy.

2 | METHODS

2.1 | Study design

This is a descriptive cohort study. Caldicott Guardian[20] approval was obtained from NHS Tayside information governance services in order for nominated individuals, who are members of the clinical care team for PLHIV in NHS Tayside, to access the relevant clinical database/records for the purposes of the study and create an anonymized database using Microsoft Excel 2013 (ref: IGTCAL 5677). This database was password protected and stored on a secure, regularly backed-up server.

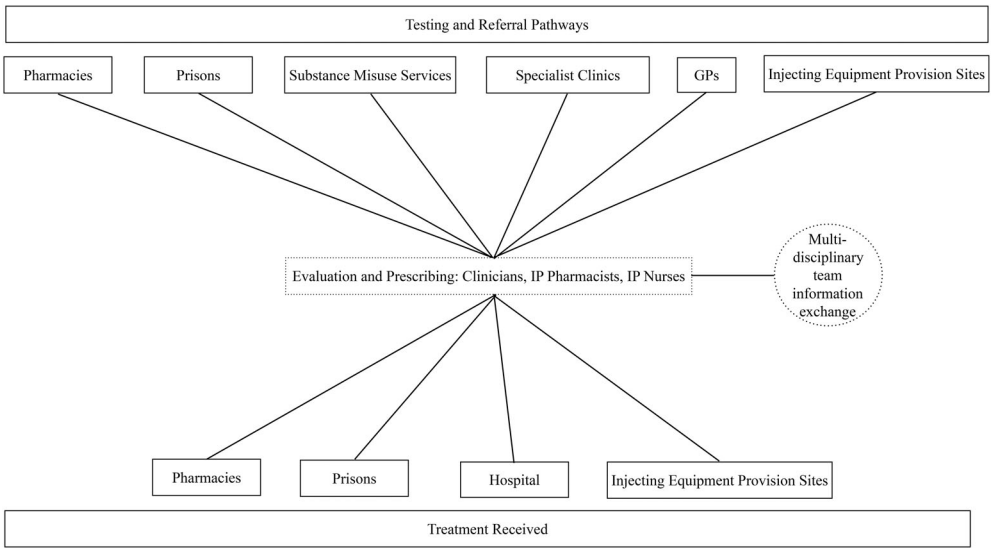

FIGURE 1 HCV testing and treatment services in NHS Tayside. GP, general practitioner; HCV, hepatitis C virus; IP, independent prescriber

2.2 | Setting

NHS Tayside is a health board in Scotland serving some 400 000 people, of which an estimated 2761 are current PWID (defined as self-reported ever having injected drugs).

A team of infectious diseases physicians, trained HIV nurses, and pharmacists care for all PLHIV, including PWID, in NHS Tayside using an integrated care pathway. The HCV-HIV co-infected population are managed by the infectious diseases team with input from hepatologists via a weekly multi-disciplinary team meeting, and HCV specialist nurses embedded in injecting equipment provision sites and opiate substitution therapy clinics. It is routine practice to screen PLHIV for hepatitis B virus and HCV at initial contact with services. HCV testing is then repeated annually in multiple settings (Figure 1) if there are ongoing risk factors, or ad hoc if alanine transaminase is elevated (≥55 IU/L). Depending on the setting, testing is either by venous blood sample or dry blood spot test, which has been shown to be particularly effective in testing PWID for HCV in Tayside and linking them to care.[21]

All routine virology testing for the region is performed in a central laboratory, so all data from all known patients with HCV-HIV co-infection in Tayside is routinely collected on an electronic clinical database. Patient characteristics, test results, and treatments are recorded by the treating physicians/healthcare staff.

2.3 | Participants

All adults (18 years or older) recorded on the NHS Tayside clinical database with a diagnosis of HIV and a positive HCV result (IgG or PCR) were screened initially for inclusion. Those with a positive HCV IgG, but without positive HCV PCR test were excluded from the study cohort. Those with both a diagnosis of HIV and a positive HCV PCR test result were eligible for analysis and included in the final cohort.

Data were censored at October 31, 2019.

2.4 | Data sources

Data on: PWID in Tayside; prevalence of HCV among PWID; demographic data; laboratory results; imaging reports; and prescription records were exported from the NHS Tayside clinical database. Data on current HCV testing among PLHIV in NHS Tayside was obtained from the NHS Tayside Public Health database. Once obtained, all data was anonymized and saved to a password-protected Microsoft Excel 2013 workbook, stored on a secure NHS server. Patient identifiable information was not utilized in the analysis.

2.5 | Statistical methods

Annual and cumulative treatment uptake was calculated for the cohort eligible for HCV treatment (HCV PCR positive, alive, and resident in the area). Treatment outcome was defined as sustained viral response at least 12 weeks post treatment (SVR^{12}), virologic failure (nonresponse or relapse), or nonvirologic failure (death, lost to follow up or missing SVR^{12} data). If treated for HCV but death occurred prior to SVR^{12} test, individuals were considered an unsuccessful treatment, as it would have been inappropriate to include deceased individuals in the cohort of successful treatments. Relapse is defined as undetectable HCV RNA by the end of treatment, but detectable following treatment cessation. Nonresponse is a detectable HCV RNA above the limit of detection (10 IU/mL) throughout treatment. Reinfection was defined as quantifiable HCV RNA positivity after a negative SVR^{12}. Annual HCV RNA testing is offered to PLHIV cured of HCV, but where a recent test was not available, the most recent post-SVR12 test was used. Reinfection incidence was calculated in person-years. Standard descriptive statistics were utilized. Confidence intervals were calculated assuming the data arose from a Poisson distribution. Statistical analysis was undertaken using SPSS (IBM SPSS v.22).

3 | RESULTS

3.1 | Participants

Between January 2001 and October 2019, 76 PLHIV were diagnosed to have either past (HCV IgG positive, HCV RNA negative) or current (HCV RNA positive) HCV in this cohort. Fifty-eight (76%) had current HCV infection. Four (7%) moved from the area and five (9%) died prior to commencing HCV therapy. This left 49 (84%) PLHIV who were assessed and eligible for HCV treatment with the clinically favored treatment method at time of assessment, based on their clinical characteristics (eg, fibrosis markers, viral parameters, liver function tests, safety bloodwork, HCV treatment history, HIV viral suppression). The 18 PLWH who were HCV IgG positive, PCR negative, were presumed to have spontaneously cleared their HCV infection (Table 1).

Time of follow up was 372 person years (py; median follow up time: 7 years, IQR 2,12). Five participants died during follow-up after initial failed treatment (mortality rate 1.34 per 100 py; 95% CI 0.2-2.5) of which none were known to be liver related (mixed drug overdose n = 2, unknown n = 3). Two patients were lost to follow-up (0.54 per 100 py; 95% CI (−0.7-0.7): nonengager n = 1 and missing post-treatment HCV RNA n = 1.

3.2 | Descriptive data

Individuals were predominantly male (n = 30, 61%). Mode of HCV transmission, which is self-reported by patients to the treating physician and recorded on the clinical database, was documented as injecting drug use (n = 39, 80%), heterosexual contact in female individuals (n = 5, 10%), migration from another country (n = 2, 4%), contaminated blood products (n = 2, 4%), and unknown (n = 1, 2%). Median Fibroscan score for the analyzed cohort was 11.9, and 16 were diagnosed with cirrhosis (Fibroscan of ≥12.5 kPa; Table 1).

TABLE 1 Demographic data for the cohort of PLHIV found to be HCV IgG positive and pretreatment features of the HCV-HIV co-infected population

Demographic table	
Characteristic	**PLHIV and HCV IgG positive (n = 76)**
Median age at HCV diagnosis (IQR)	38 (33-44)
Gender—n (%)	
Male	50 (65.8)
Female	26 (34.2)
Characteristic	HCV-HIV co-infected population (n = 49)
On combination HIV therapy—n (%)	49 (100)
Mode of HCV transmission—n (%)	
Injecting drug use	39 (80)
Sexual exposure	5 (10)
Other	5 (10)
HCV genotype—n (%)	
1	16 (33)
2	1 (2)
3	32 (65)
Median Fibroscan® score (IQR) in KPa	11.9 (6.6-17.6)
Cirrhosis—n (%)	16 (33.3)

Abbreviations: HCV, hepatitis C virus; IQR, interquartile range; IgG, immunoglobulin G; PLHIV, people living with HIV.

3.3 | Main results

Of the 49 co-infected PLWH, 48 commenced HCV treatment, 44 achieved SVR[12] and 5 died post-treatment (Figure 2).

Given the treatment period, most HCV treatments were with Peg-IFN containing regimens (n = 30). Virologic or nonvirologic failure occurred in 12/30 (40%) with Peg-IFN containing regimens, of those nine (75%) had a second course of treatment to cure HCV, and all obtained SVR[12] (Figure 2, Table 2). The remaining three died before they could be retreated.

Between 2001 and 2019, 10 people initiated more than one course of HCV therapy. Nine were initially treated with Peg-IFN containing regimens, while one had been treated with DAAs. All 10 individuals achieved SVR[12] following retreatment.

Annual proportions of PLHIV diagnosed and treated for HCV increased from 3.57% in the interferon era to 66.67% per year in the interferon free DAA era (Table 3 and Figure 3). SVR[12] was achieved in all treated individuals in 2017, 2018, and 2019. Overall SVR[12] for the cohort is 75% (CI 63.9-83.1; 44/58 treatment courses). Proportion of the cohort achieving SVR[12] with DAA therapy, including treatment experienced, was 92% (CI 81.8-102.2; 25/27 treatment courses). Only one individual with known HCV-HIV coinfection is treatment naïve and remains to be treated in Tayside, with efforts to engage them in care ongoing. None of the remaining cohort of PLHIV alive and resident in Tayside require re-treatment for HCV at this time.

Reinfection was reported in one individual who initially attained SVR[12] following Peg-IFN based treatment who was subsequently successfully retreated with DAAs. Reinfection incidence is calculated at 0.2 per 100 person years (CI −0.3 to 0.7) in the cohort.

Currently, 361 PLHIV receive HIV care in Tayside: 348 (96%) have been HCV tested and are aware of their status; 13 (4%) have no HCV test recorded. A total of 256 were tested through HIV clinics; 20 through hospital sexual health drop-in clinic; 19 through their GP; 15 as hospital inpatients; 11 in hospital outpatients; 2 in assistant conception services; 2 in mental health services; 2 in maternity services; and 1 in drug services. The source of 20 HCV tests were unclear.

4 | DISCUSSION

4.1 | Key results

The data presented here illustrate a long term, concerted multi-stakeholder effort to microeliminate HCV infection among PLHIV in NHS Tayside which, following introduction of DAAs, meets the criteria set out in the guideline paper on microelimination of HCV.[15]

This study makes a novel contribution to the existing literature[16-19] as it is a retrospective analysis of real-world outcomes which spans nearly 20 years, in persons whose most common mode of HCV transmission is injecting drug use. This differs from published studies on microelimination of HCV among PLHIV from Switzerland and the Netherlands[18,19] which are primarily focussed on MSM. Injecting drug use is recognized as a major risk factor for HCV-HIV coinfection,[22] and among PWID there is considerable risk of reinfection with HCV post-SVR[12].[23] However, the low incidence of HCV re-infection in this predominantly PWID cohort suggests the general risk of HCV re-infection may be lower in PWID than that observed in HCV-HIV co-infected MSM.[18,24]

The introduction of DAAs reduced the burden of HCV infection among PLHIV from 2014 onward, similar to other findings,[17] with cumulative proportions of PLHIV co-infected with HCV both treated and cured increasing compared to the Peg-IFN era (Table 3, Figure 3). The overall SVR[12] proportion for the cohort is perhaps somewhat below what could be expected given published SVR rates in PWID in excess of 90%.[25-27] However, this can be explained by the relatively higher number of Peg-IFN treatment observed. The DAA-only SVR12 rate is more in line with contemporary expectations.

Retreatment of individuals who became either reinfected with HCV post-SVR[12] or experienced virologic/nonvirologic failure was evident in this cohort. Of the individuals who received more than one course of HCV treatment, SVR[12] was achieved in all instances of retreatment. This demonstrates that individuals who have previously undergone HCV treatment should be offered retreatment which is not contingent on discriminatory parameters,[28] especially in the context of microelimination, and particularly given emerging evidence of successful regimens for those who previously failed NS5A-containing regimens.[29]

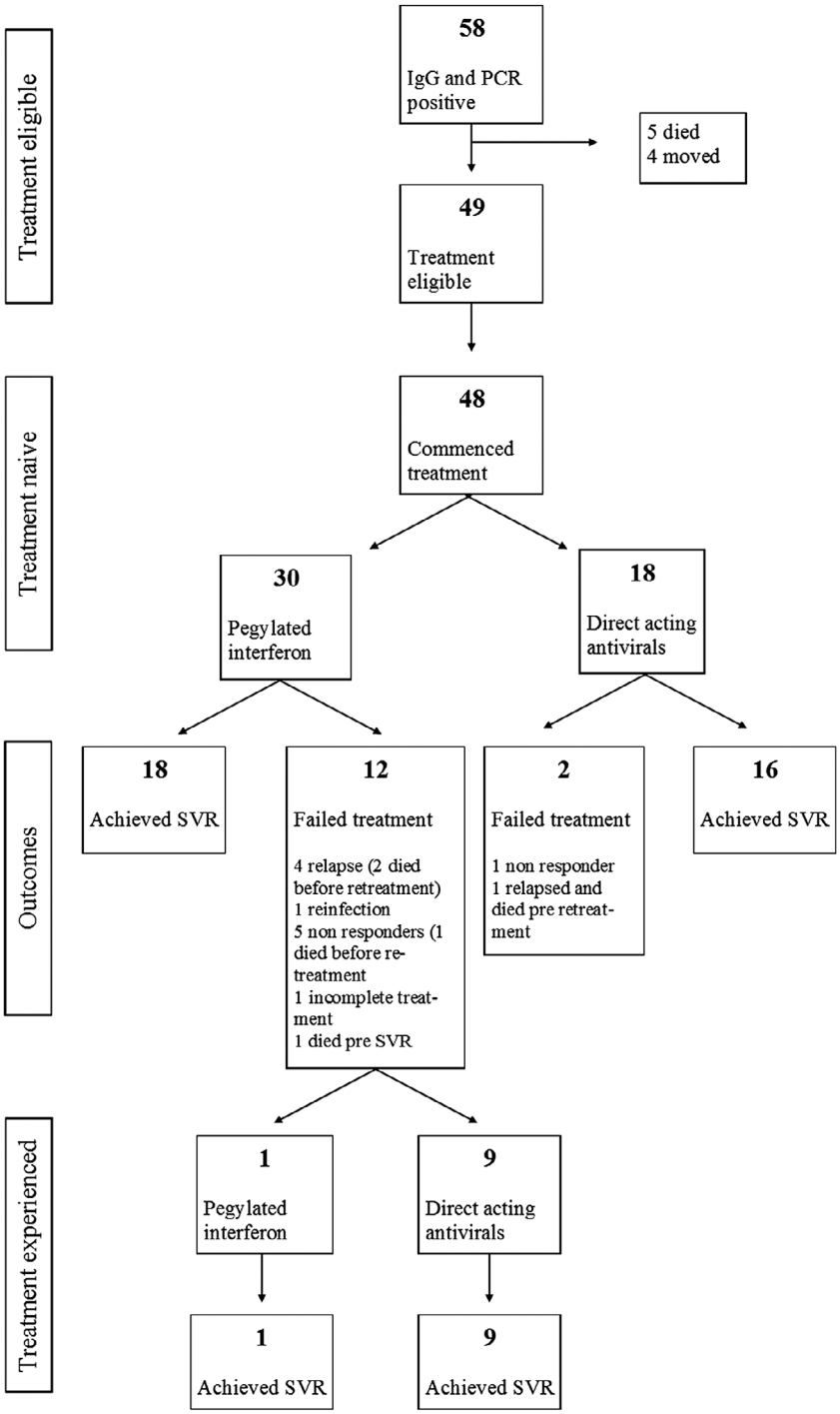

FIGURE 2 HCV treatment outcomes for PLHIV in NHS Tayside 2001 to 2019. HCV, hepatitis C virus; IgG, immunoglobulin G; PCR, polymerase chain reaction; SVR, sustained viral response

NHS Tayside's integrated multistakeholder care pathway for HCV among PLHIV has been key to progressing microelimination in this cohort, with BBV tests being conducted in nine different services (Figure 1). Integrating care pathways for HCV have been successful in several discrete settings,[30-32] and this study adds to the evidence for co-location HCV care in related services at a regional level. Routine HCV testing among PLHIV through diverse services ensures ongoing monitoring of primary and reinfection.

The low loss to follow up in this cohort, and the willingness of PLHIV to accept retreatment for HCV, indicates strong levels of engagement and a trusting relationship with the clinical team among PLHIV in NHS Tayside, factors recognized as essential to successful management of chronic health conditions like HIV[33] and HCV. The real-world data presented here indicate that regional microelimination of HCV-HIV coinfection can be advanced with an integrated model of care, and HCV case-finding recommendations[34] that encourage testing and DAA treatment occurs close to the patient in community settings.

5 | LIMITATIONS

The clinical data analyzed in this study are generated from routine clinical practice and therefore open to potential mischaracterization at

the time of input by the healthcare staff recording the data. Any data queries were addressed to staff who entered that data where possible. Where queries could not be resolved, data was presumed accurately recorded. Cause of death could not be confirmed in three individuals.

The study cohort is a small localized sample size, but is likely to be representative of the wider HCV-HIV coinfected cohort in Scotland, or the United Kingdom, because of the population mix and dispersion in the region. This cohort size may limit the generalizability of the findings; especially for other cohorts of coinfected PLHIV who may not have become infected with HCV via injecting drug use.

The study cohort may be biased toward those PLHIV who are more likely to engage with healthcare services, and may not represent the entire burden of HCV-infected PLHIV residing in NHS Tayside, however, only small numbers of patients will not have presented to services as a consequence of their HIV infection because access to services is both comprehensive and community based. Furthermore, Scotland has already attained UNAIDS 90-90-90 targets,[14] indicating the burden of unknown infection is likely to be low.

TABLE 2 HCV treatment uptake and outcomes among PLHIV in NHS Tayside, 2001 to 2019

	Interferon ± ribavirin ± 1st generation DAA (n = 31)	Interferon-free regimens (n = 27)
Prescribed treatment course completed—n (%)	29 (93)	26 (96)
SVR 12—n (%)	19 (61)	25 (92)
Virological failure—n (%)		
Non response	5 (16)	0
Relapse	4 (13)	1 (4)
Non virological failure—n (%)		
Death	1 (3)	1 (4)
Lost to follow up/missing SVR	1 (3)	1 (4)

Note: Data includes treatment naïve and treatment experienced.
Abbreviations: DAA, direct acting antivirals; PLHIV, people living with HIV; SVR, sustained viral response.

6 | INTERPRETATION

The data presented here show that there was an increase in the proportion of coinfected individuals both initiating and successfully completing treatment for HCV after the introduction of DAAs in NHS Tayside. Access to DAAs, and co-locating BBV services as part of a multi-stakeholder strategy, substantially aided efforts to micro-eliminate coinfection in the region, and should be considered elsewhere.

Our data indicate that widespread, sustained and non-discriminatory access to DAAs be prioritized for HCV-HIV co-infected populations, including PWID and treatment-experienced individuals, if WHO 2030 goals are to be realized. The high proportion of individuals achieving a cure following retreatment indicates that it is feasible and desirable to retreat HCV in co-infected PWID.

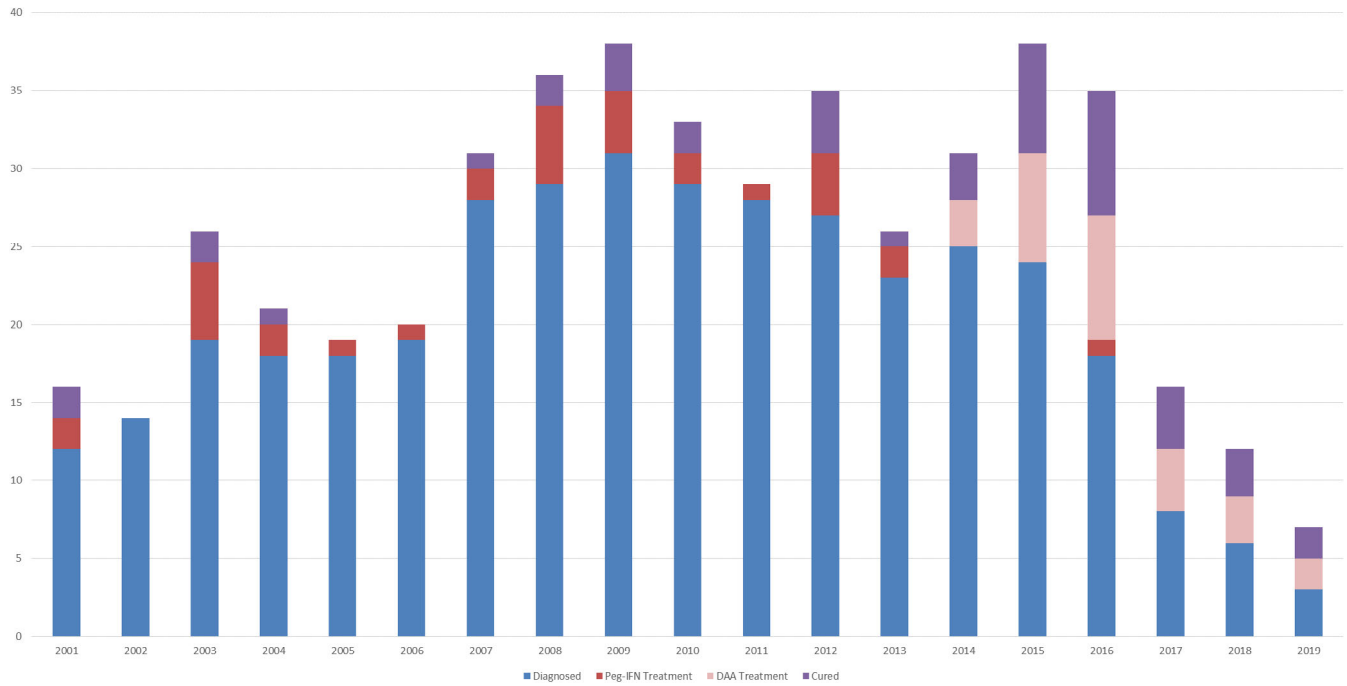

FIGURE 3 Annual HCV diagnosis, treatment and cure in PLHIV in NHS Tayside 2001 to 2019. Note introduction of DAAs in 2014, and decrease in diagnoses of new infections thereafter. DAA, direct acting antivirals; HCV, hepatitis C virus; Peg-IFN, pegylated interferon

TABLE 3 Tabulated annual HCV diagnosis, treatment, and cure among PLHIV in NHS Tayside 2001 to 2019

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Diagnosed	12	14	19	18	18	19	28	29	31	29	28	27	23	25	24	18	8	6	3
Treated with Peg-IFN	2	0	5	2	1	1	2	5	4	2	1	4	2	0	0	1	0	0	0
Treated with DAAs	0	0	0	0	0	0	0	0	0	0	0	0	0	3	7	8	4	6	2
Proportion treated[a]	17%	0%	26%	11%	6%	5%	7%	17%	13%	7%	4%	15%	9%	12%	29%	50%	50%	50%	67%
Cured	2	0	2	1	0	0	1	2	3	2	0	4	1	3	7	8	4	3	2

[a]Proportion of diagnosed, treatment eligible people treated per year.

Abbreviations: DAA, direct acting antivirals; Peg-IFN, pegylated interferon; PLHIV, people living with HIV.

It is apparent that a co-located integrated care pathway can effectively monitor for reinfection in defined geographic areas. Reinfection incidence was low in this cohort, and testing rates are high among PLHIV in NHS Tayside. The data presented here add to the evidence supporting integration of BBV services when undertaking a HCV microelimination strategy at a regional level.

CONFLICT OF INTEREST

John F. Dillon has received personal honoraria for lectures and institutional research grants from MSD, AbbVie, Gilead, Roche, and Janssen. All authors declare no conflict of interest.

TRANSPARENCY STATEMENT

Christopher Byrne affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

The data underpinning this study were obtained from routinely updated NHS health records in line with approval granted by the NHS Caldicott Guardian. The individuals to whom the data pertains did not explicitly consent to its use for research purposes. Therefore, it is not possible for the authors to share this data. However, interested parties can make specific requests to NHS Tayside Information Governance by email on: informationgovernance.tayside@nhs.net.

AUTHOR CONTRIBUTIONS

Conceptualization: Christopher Byrne

Data Curation: Emma Robinson, Christopher Byrne, Nikolas Rae

Statistical Analyses: Emma Robinson

Data Visualization: Christopher Byrne and Emma Robinson

Writing-Original Draft Preparation & Review: Christopher Byrne

Supervision: John F. Dillon

Methodology: All authors

All authors have read and approved the final version of the manuscript.

Christopher Byrne had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

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