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Increased case-finding and uptake of direct-acting antiviral treatment essential for micro-elimination of hepatitis C among people living with HIV

Introduction

Since the introduction of Direct Acting Antiviral (DAA) treatment for hepatitis C virus (HCV) infection, with shorter treatment duration and cure rates exceeding 95%, elimination of the virus is now possible.[1,2] The World Health Organization (WHO) has set the goal of reducing HCV mortality by 65% and new chronic HCV infections by 80% by 2030.[3,4] Micro-elimination of HCV in key populations has been proposed as a pragmatic approach to the overall elimination goal.[5] Where health systems may not be prepared for the scale up of prevention, testing and screening required for full-scale elimination, micro-elimination provides a mechanism for incremental progress towards elimination.[6] This involves the elimination of HCV in a defined population, for example people in specific settings, risk groups or those with co-infections, in the recognition that different populations may need different services. A key population for micro-elimination is people living with HIV (PLHIV) and co-infected with HCV. [7,8]

Of the estimated 36.9 million PLHIV worldwide, 2.3 million (6.2%) are also HCV antibody positive.[9] The prevalence of HCV antibody positivity varies significantly by risk group, ranging from 6.5% among HIV infected men who have sex with men (MSM) to 82.4% among HIV infected people who inject drugs (PWID).[10] The 2015 European Association for the Study of the Liver (EASL) recommendations on treatment of HCV prioritised DAA therapy for HCV/HIV co-infected individuals, regardless of fibrosis stage, due to drug interactions between anti-retroviral therapy and interferon-based HCV treatments.[11] Treatment in co-infected PLHIV with DAA therapy has now been shown to be as highly effective as for HCV mono-infected patients. [12-13] More recently, the British HIV

Association (BHIVA) has called for an accelerated effort to eliminate HCV among PLHIV with targets to cure 80% of all patients diagnosed with HIV and HCV co-infection by 2019, increasing to 100% by 2021.[14]

Scotland is uniquely placed to monitor progress towards micro-elimination of HCV among PLHIV targets through national surveillance of HIV diagnoses linked to HCV testing, diagnoses and treatment data. Here we demonstrate an approach to monitor progress towards elimination of HCV among PLHIV, using a combination of surveillance data and prediction modelling. These data are important to inform what progress has been made and where further effort is required to reach HCV elimination in this population.

Methods

Study Design

Through analysis of national and sentinel surveillance data, we examined extent of HCV testing, diagnosis, and treatment among the cohort of people living with diagnosed HIV in Scotland identified through the national database of HIV diagnosed individuals. Through data linkage to the sentinel surveillance HCV test database, we established factors associated with being not tested for HCV for those living in four NHS board areas and used the results from this analysis to predict the proportion not tested across Scotland. Similarly, we established the factors associated with being anti-HCV positive among those tested and used these to predict undiagnosed HCV cases. Linkage to the national HCV diagnoses database provided a cohort of patients who were diagnosed with both HIV and HCV. Linkage to the national HCV clinical database allowed for the analysis of the cascade of attendance, treatment and cure of HCV. We then used the results from these analyses to benchmark Scotland's position in regard to the BHIVA micro-elimination targets.

Data were managed and analysed using Statistical Package for Social Sciences (SPSS) Version 24.0.

Data sources

We utilised data from four sources: National database of all individuals diagnosed with HIV in Scotland since 1985; National database of all individuals diagnosed HCV antibody positive in Scotland since 1991; Sentinel surveillance database of all HCV (antibody and PCR/antigen) tests undertaken in four regions (which account for 75% of all tests undertaken in the country) since 2000; Clinical database of individuals attending appointments for treatment/management of HCV at 17/18 specialist HCV treatment clinics across Scotland

since the early 1990s; additional data on treatment of co-infected patients at the only clinic in Scotland not routinely providing individual-level clinical data was also ascertained for this analysis.[15-18] Mortality was available from linkage to the Scottish death register and migration from the Community Health Index (a population register used for healthcare in Scotland) . Appendix 1 shows an overview of the data sources and analyses undertaken in this study. Each database holds the Community Health Index number (a unique identifier allocated to each patient in Scotland), which was used to deterministically link across the databases.

Approval for linkage was obtained from the Public Benefit and Privacy Panel for Health and Social Care. Data to 31 December 2017 were analysed for each database.

Study population

Individuals were eligible for inclusion if they had a record on the HIV diagnosis database, were not known to have died as at 31 December 2017, did not have an indication that they had left Scotland, and had sufficient information for data linkage (see appendix 2). Hereafter, PLHIV will refer to these individuals living in Scotland with diagnosed HIV. Given the reduced coverage of the HCV test database in terms of geographic coverage and availability of data going back to 2000, a subset of the eligible cohort, referred to hereafter as the “HCV test cohort”, residing in the four regions with available HCV test data and diagnosed since 2000 was analysed.

Statistical Analysis

Two binary logistic regression analyses were undertaken. Covariates used in the statistical analyses are described in appendix 3. The first, using HCV test cohort, examined factors associated with not being tested for HCV. The co-factors included were: sex, HIV

transmission route, current age group, SIMD quintile, ethnicity, HIV treatment status, HIV diagnosis setting, HIV attendance, and AIDS diagnosis. Each co-factor was analysed at the univariate level and the multivariate level using a backward step-wise method. Co-factors that did not reach the 5% significance threshold were excluded. This model was used to predict the numbers not tested for the remainder of the full cohort (i.e. those not included in the HCV test cohort), which were combined with the number known not tested from the HCV test cohort to determine the overall estimated number not tested among PLHIV in Scotland.

Antibody positivity among those not tested for HCV was estimated by combining (a) prediction model using the above cofactors to predict HCV positives among PWID who were not tested and (B) for non-PWID who were not tested, the crude HCV positivity rate among those tested was used.

The second logistic regression, using the full cohort, considered factors associated with never being treated for HCV among those who had not been diagnosed with chronic HCV. The co-factors included were: sex, HIV transmission route, current age group, deprivation, HIV treatment status and source of HCV diagnosis. Co-factors that did not reach the 5% significance threshold significant impact on the model were excluded.

Estimating progress towards micro elimination

Using the results of the above analyses, progress towards the micro-elimination of HCV among PLHIV was estimated. The estimated number of PLHIV with Ever Chronic HCV was calculated by adding (1) number diagnosed with chronic HCV (past or current), (2) estimated number HCV chronic whose chronic status was unknown, (3) estimated number with undiagnosed chronic HCV. The estimated number of PLHIV with Current Chronic HCV was calculated by adding (1) estimated number with undiagnosed chronic HCV, (2) estimated number HCV chronic whose chronic status was unknown, (3) the number diagnosed HCV

chronic, never attended, treated and no SVR. Progress towards the BHIVA treatment targets was calculated as the proportion of PLHIV diagnosed with chronic HCV who had achieved an SVR.

Results

Characteristics of study population

The study cohort included 5018 (55%) of all HIV diagnosed patients in Scotland. Appendix 1 shows the number of patients excluded from analysis based on the exclusion criteria. Around three quarters of the cohort were male (72%), older than 40 years old in 2017 (74%) and white ethnicity (White-Scottish and White-Other) (76%). More than half (56%) of those with SIMD available resided in the most deprived two SIMD quintiles, compared with 40% of the general population. The most common HIV transmission group was MSM (45%), followed by heterosexual (39%) and PWID (11%). The most common diagnosis setting was GUM clinics (40%) followed by hospital (32%) and general practice (10%).

HCV test uptake

A total of 2939 (59%) from the study population were eligible for the sub-analysis of HCV test uptake and one fifth (20%) had never been tested for HCV during the study period. Table 1 shows key characteristics of the HCV test cohort. The proportion never tested for HCV test uptake was particularly high among those not on HIV treatment (57%), those in the “Other/NK” risk group (30%), and “White – Other” ethnicity (31%).

In the first multivariate regression analysis of factors associated with never being tested for HCV, the final model included current age group, deprivation, ethnicity, HIV treatment status, HIV diagnosis setting, HIV attendance and AIDS diagnosis status. The odds of never being tested for HCV were highest in those who were not on HIV treatment (adjusted Odds Ratio = 7.21, 95% CI 5.15- 10.10), diagnosed in a GUM Clinic (aOR = 3.44, 95% CI 2.68 - 4.40), are in the “Other” ethnicity group (aOR = 3.46, 95% CI 2.10 - 5.70), and those residing in the least deprived SIMD quintile (aOR = 1.83, 95% CI 1.33 - 2.52). Using this model to

predict the number never tested from the remaining 2079 (41%) of the full cohort, 221 (11%) were predicted as having not been tested. An estimated 797 (16%) of the full cohort were never tested for HCV (Figure 1). Of those not tested for HCV, 100 were estimated to be HCV antibody positive (62 PWID and 38 non-PWID) (Appendix 4).

Diagnosed HCV in the study population

Table 2 shows HCV diagnoses among HIV diagnosed patients in Scotland. There were 613 (12% of 5018) were also diagnosed HCV antibody positive. The highest proportions co-infected were among PWID (67%), those diagnosed in “other” settings (20%) and those living the most deprived SIMD quintile (16%), while the lowest proportions co-diagnosed were among those who acquired their HIV through heterosexual transmission (4%), MSM (5%), those of non White-Scottish ethnicity (6%) and those diagnosed in GUM clinics (75). Of the 613 co-infected patients, 485 (79%) were diagnosed Ever Chronic HCV (either past or current chronic infection). In a further 44 (7%) co-infected patients, chronic status was not known, while 84 (14%) had spontaneously resolved their infection.

Attendance at specialist services and HCV treatment

Of the 485 Ever Chronic HCV group, 441 (91%) had attended a specialist HCV treatment clinic. Of those who had attended 293 (66%) had been treated at least once and 249 (85%) of these had achieved an SVR. The odds of never being treated for HCV (Table 3) were highest in those who were not on HIV treatment (aOR= 3.60, 95% CI 1.59 - 8.15), those residing in the most deprived areas (aOR=2.64, 95% CI 1.04 to 6.71), and PWID (aOR=2.09, 95% CI 1.04 to 3.78).

Progress towards micro-elimination of HCV among HIV diagnosed patients

Figure 1 shows the estimated numbers of chronic HCV infections (ever and current) among people living with diagnosed HIV in Scotland. It is estimated that 586 individuals were Ever Chronic HCV and that 337 had Current Chronic HCV. The proportion of Ever Chronic HCV infections among HIV diagnosed patients that had been diagnosed was 83% (485/586). With regard to the BHIVA targets, 51% (249/485) of those with diagnosed Chronic HCV and HIV had been cured of their HCV by the end of 2017 and 91% (441/485) had been assessed at a specialist HCV treatment service. Of all Chronic HCV infections (diagnosed and undiagnosed) among HIV diagnosed patients, 42% (249/586) had been cured of their HCV.

Discussion

The Scottish Government has recently committed to elimination of hepatitis C as a public health concern in Scotland by 2024.[19] In 2018, the British HIV Association (BHIVA) recommended an accelerated effort to eliminate HCV among people living with HIV with targets to cure 80% of all co-infected patients by 2019 (with 100% of patients assessed for therapy) increasing to 100% by 2021.[14] Utilising a variety of surveillance initiatives for blood borne viruses in Scotland, this is the first study to examine progress towards micro-elimination of HCV among PLHIV at a national level, including estimating the extent of undiagnosed infection.

In our analysis of HCV testing, it was predicted that around 15% of PLHIV in Scotland have never been tested for HCV. BHIVA guidelines recommends that all “patients have an HCV antibody test when first tested HIV antibody positive” and patients with repeated high-risk exposures should be tested at least twice a year. [20] Similarly, the Scottish Intercollegiate Guidance Network (SIGN) guideline recommends HCV testing for all PLHIV and annual testing for those who continue to be at risk. [21] We estimate that around 70 PLHIV of those who have never been tested for HCV have undiagnosed chronic HCV. Diagnosing all co-infections is essential for micro-elimination and efforts should be made to increase and maintain HCV testing of PLHIV, particularly those attending specialist HIV services or continue to inject drugs.

Overall, 11% of PLHIV were also diagnosed HCV antibody positive. HCV positivity was highest among people who inject drugs (PWID) at 49%. PWID represent 63% of those diagnosed with both HIV and HCV despite being only 14% of the PLHIV population. This is consistent with the epidemiology of HCV among PWID and highlights a key group for the micro-elimination of HCV in PLHIV.[5,6] Despite this, only 59% of PWID with chronic

HCV and who attended HCV treatment services had been treated for their HCV and co-infected PWID were almost twice as likely not to be treated for their HCV than those who acquired HIV through heterosexual transmission.

Men who have sex with men (MSM) represent the largest risk group among PLHIV and 4% were also diagnosed HCV antibody positive. Outbreaks of sexually transmitted HCV among HIV positive MSM have been well documented globally, including in other parts of the United Kingdom.[22,23] In this study, more than three quarters of HIV positive MSM had ever been tested for HCV. With the introduction of Pre-Exposure Prophylaxis (PrEP) to prevent HIV infection, an increase in condomless sex is likely among MSM engaged in the highest risk activity, which may lead to an increase in sexually transmitted HCV. [24,25] Regular HCV testing in this group is essential to diagnose and treat patients infected with HCV and prevent onward transmission.

Of PLHIV diagnosed with chronic HCV, 90% had attended a specialist HCV treatment clinic for assessment by the end of 2017, which, while high, suggests the BHIVA target of 100% of co-infections assessed by April 2019 may have been missed. Of those who had attended HCV treatment services, one third had not received any treatment for their HCV. Only half of those with chronic HCV had achieved an SVR by the end of 2017. This indicates a key challenge in achieving the BHIVA treatment targets of 80% treated by 2020 target and for micro-elimination in general.

There are several reasons why co-infected PLHIV may have sub-optimal HCV treatment uptake despite being engaged with other services. Response rates for co-infected patients treated with pegylated interferon and ribavirin were 10-20% lower than HCV monoinfected patient and drug interactions between HCV and HIV treatments had been documented.[26] Either of these factors may have had an impact on treatment uptake among co-infected

patients but with the introduction of DAA therapy, these particular barriers have been overcome.[27]

To meet the BHIVA treatment target, significant increase of treatment among co-infected patients is essential, which highlights the challenges for micro-elimination of HCV among PLHIV. Scotland has already seen a significant scale up of treatment for HCV in recent years as a result of the Hepatitis C Action Plan.[28] In 2006, less than 10% of those with chronic infection had attended a specialist HCV treatment clinic and around 450 were initiated onto treatment per year. By the end of the Action Plan in 2010, the numbers treated per year had more than doubled and to achieve the Scottish Government elimination goal this will increase to 3,000 patients initiated onto therapy per year.[19]

In comparison to these increases, the number of patients needed to be treated to eliminate HCV among PLHIV is relatively small and achievable. Between 2015 and 2017, HIV co-infected patients were among the groups prioritised for DAA treatment in Scotland, along with patients with F2-F4 hepatic fibrosis, patients with severe extra-hepatic manifestations of HCV and/or patients with significant psychosocial morbidity as a consequence of HCV (with all patients eligible for DAA treatments since 2017).[29] That DAA treatment has been available for several years, the majority are in contact with HIV services and treatment uptake remains relatively low represents a system failure. The reasons for this are likely multi-faceted including: HIV and HCV services being separated in different healthcare silos, increased pressures on HIV and sexual health services, lack of knowledge that the previous clinical barriers to treatment have been overcome and patients not prioritising their HCV infection. At the very least, referral pathways between HIV services and specialist HCV treatment clinics should be reviewed to ensure these reflect current treatment guidance and facilitate access to HCV treatment. Education for staff at HIV services and PLHIV on DAA

and HCV elimination may be required and delivery of HCV treatment through HIV services could be considered as a method of achieving micro-elimination.

BHIVA recognised that while rapidly increasing treatment is possible the challenges of treating the most vulnerable patients, such as those who are currently homeless, may also require some short-term specialist services.[14,30] The importance of these most vulnerable groups to the HCV elimination goals cannot be overstated. The recent outbreak of HIV among PWID in Scotland's largest city has clearly demonstrated how quickly blood borne viruses can spread among injecting networks particularly among homeless people and those who inject in public. More than 90% of those infected with HIV in the outbreak were co-infected with HCV.[31]

As this study starts with the HIV diagnosis database, it has not been possible to consider here patients who are infected with HIV but remain undiagnosed. It is, however, estimated that the undiagnosed HIV population is low in Scotland.[16] A study in England covering the pre-DAA era examined co-infection from the other perspective, i.e. starting with HCV diagnosed patients and examining factors associated with HIV infection, found that rates of co-infection were highest among MSM and reported lower co-infection rates than we describe.[32] These differences may relate to the sexually transmitted outbreaks of HCV among MSM that have been described in England but, so far, have not been seen in Scotland and the HIV outbreaks among PWID in Scotland that have not been observed in England.

Our analysis has been limited to the data collected on the HIV and HCV surveillance databases. There are likely numerous factors beyond those analysed here that may impact on HCV testing or treatment among PLHIV. This was a particular issue in our attempts to predict the number of HCV infections among those who had not been tested. Only PWID status was associated with positivity and so it was not and so it was not possible to use a

prediction model for positivity among the non-PWID group. This has affected the precision of the undiagnosed HCV estimates and these should be interpreted accordingly. Similarly, we may have underestimated the extent of migration within the study cohort as we know that, for example, 40% of those diagnosed with HIV in 2017 were infected outside of Scotland.[15] Only those reported as being known or presumed to have migrated were excluded.. We have not been able to determine the individual reasons why someone may have chosen not to accept treatment or the specific support that this patient group may require to increase treatment rates. Further qualitative work may provide insight into this subject. All linkage studies carry the possibility for error and there may be records that have been matched incorrectly and others that have not been matched despite belonging to the same person.[33] However, the use of this study design has allowed for a rapid assessment of Scotland's position in regards to micro-elimination of HCV among PLHIV and progress towards the BHIVA targets and can be repeated to monitor progress towards elimination.

Conclusion

Bringing together a variety of data sources, we have demonstrated an approach to measuring progress towards micro-elimination in people living with HIV. We found that a significant minority of PLHIV had yet to be tested for HCV despite guidance recommending annual testing for those who continue to be at risk. This should be included in the routine monitoring of CD4 and viral loads. Whilst the vast majority have had contact with specialist HCV services, only half had been successfully treated by the end of 2017, two years after the prioritisation of DAAs for PLHIV in Scotland. The co-infected population in Scotland is relatively small, mainly among PWID and most of the untreated patients are already engaging with HIV services. To achieve micro-elimination of HCV in PLHIV in Scotland a sustained effort to increase treatment uptake is essential.

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