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Evidence of continued injecting drug use after attaining sustained treatment-induced clearance of the hepatitis C virus: implications for reinfection

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ABSTRACT

Background: People who inject drugs (PWID) are at the greatest risk of hepatitis C virus (HCV) infection, yet are often denied immediate treatment due to fears of on-going risk behaviour. Our principal objective was to examine evidence of continued injecting drug use among PWID following successful treatment for HCV and attainment of a sustained viral response (SVR).

Methods: PWID who attained SVR between 1992 and June 2012 were selected from the National Scottish Hepatitis C Clinical Database. Hospitalisation and mortality records were sourced for these patients using record linkage techniques. Our primary outcome variable was any hospitalisation or death which was indicative of injecting drugs post-SVR.

Results: The cohort comprised 1170 PWID (mean age at SVR 39.6y; 76% male). The Kaplan Meier estimate of incurring the primary outcome after three years of SVR was 10.59% (95% CI, 8.75 – 12.79) After adjusting for confounding, the risk of an injection related hospital episode or death post-SVR was significantly increased with advancing year of SVR: AHR:1.07 per year (95% CI, 1.01 – 1.14), having a pre-SVR acute alcohol intoxication-related hospital episode: AHR:1.83 (95% CI, 1.29 – 2.60), and having a pre-SVR opiate or injection-related hospital episode: AHR:2.59 (95% CI, 1.84 – 3.64).

Conclusion: Despite attaining the optimal treatment outcome, these data indicate that an increasing significant minority of PWID continue to inject post-SVR at an intensity which leads to either hospitalisation or death and increased risk of reinfection.

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Highlights:

- We followed-up a nationally representative cohort of 1170 PWID who had attained SVR
- Data linkage was used to examine injection-related morbidity/mortality events
- An increasing minority of our cohort had a post-SVR injection-related event
- Continued follow-up and promotion of harm reduction is warranted post-SVR in PWID
- The approach adopted here can be used to inform on trends in HCV reinfection risk

1. Introduction

It is well established that people who inject drugs (PWID) are at the greatest risk of hepatitis C virus (HCV) infection. Globally, there are an estimated 16 million PWID who are currently injecting (Mathers et al., 2008) –of these, 10 million are estimated to have been infected with HCV (Nelson et al., 2011). Chronic HCV infection is a major cause of liver-related morbidity and mortality but can be cleared with antiviral treatment and establishment of sustained viral response (SVR). Currently, there is low initiation of HCV antiviral treatment among PWID which likely relates to concerns of adherence to and reinfection post-treatment (Martin et al., 2013; Iversen and Maher 2012). Regardless, recent studies have indicated treatment outcomes to be acceptable and risk of HCV reinfection to be relatively low among PWID, albeit based on only a few small-scale studies conducted among selected populations in clinical and harm reduction settings often with limited follow-up (Aspinall et al., 2013; Arain & Robaey, 2014; Grady et al., 2013). Modelling work has further demonstrated that treating PWID is cost-effective and has the potential to reduce HCV transmission and prevalence in this population (Martin et al., 2011a, 2013). Therefore, recommendations state that treatment is not to be withheld from an individual based on injection status alone (EASL, 2015).

After being deemed one of the greatest public health challenges of our time, HCV was made a priority by the Scottish Government and a comprehensive Action Plan was formulated to curb the predominately injecting-related epidemic (Chisholm, 2004; Scottish Government, 2008). As a result, the overall number of people initiated on antiviral therapy in Scotland more than doubled between 2007 and 2010 with ~1000 now treated per year and the vast majority (>80%) of these report having ever injected drugs (HPA, 2013).

Given this recent and anticipated future upscale in treatment provision among PWID a better understanding is needed of the injecting risk behaviours and potential for reinfection post-SVR. Our principal objective, therefore, was to establish evidence and predictors of continued engagement in injection drug use post-SVR using a record-linkage approach involving both HCV treatment and injecting-related hospitalisation data for a large nationally representative cohort of over 1000 PWID.

2. Methods

2.1 Study Population, data sources, and linkage procedure

This paper utilised a retrospective cohort of Scottish PWID derived from the HCV Clinical Database using data linked from four additional national databases. Health Protection Scotland (HPS) holds and maintains individual patient data for all HCV diagnosed persons who attended a specialist centre for HCV treatment and management across Scotland, referred to as the HCV Clinical Database. This database includes information on patient demographics, virology, treatment episodes, epidemiological exposures, and liver disease investigations. Inclusion criteria for the study were a history of injection drug use, SVR attained by June 2012, and sufficient identifiers for record-linkage. To enable further database linkage (described below), the HCV Clinical Database was first linked to the Scottish HCV Diagnosis Database, as previously described (Innes, et al., 2011); this linkage also allowed for scrutiny of patient record accuracy, such that patients were dropped if flaws in treatment records were detected (e.g. missing diagnosis dates [n=68] or nonsensical treatment dates [n=95]).

Hospital episode data were obtained by sourcing Information Services Division (ISD) Scotland's Scottish Morbidity Records (SMR) 01 and 04, which provide general, non-obstetric hospital discharge data and psychiatric hospital admissions data respectively. Hospital episodes are coded using the World Health Organisation's International Classification of Disease (ICD) Ninth Revision for all hospitalisations prior to 1996, and Tenth Revision for hospitalisations thereafter. SMR records include six possible diagnostic fields, all of which were included in analysis.

Mortality data were obtained through sourcing deaths registrations collated by National Records of Scotland. Date and up to eleven causes of death are recorded for each registered death using ICD-9 and ICD-10 codes.

2.2 Linkage Procedure

ISD Scotland annually link the Scottish HCV Diagnosis Database to SMR and deaths data. This probabilistic linkage technique is estimated to have a rate of false positives or false negatives under 5% (Kendrick & Clarke, 1993); the probabilistic linkage has also been previously described (McDonald et al., 2008).

Thereafter, this linked dataset, containing SMR/deaths data on all HCV diagnosed persons, was transferred to HPS and combined with the Clinical and Diagnosis dataset via the HCV Diagnosis Database record number to enable extraction of hospitalisation and mortality data for all those who had attended a specialist clinic for HCV. The final linked dataset included all relevant

demographic, behavioural, morbidity, and mortality data for 1170 Scottish PWID who had received antiviral treatment for HCV and attained SVR in the over 20 year period between 1992 and June 2012.

2.3 Outcome Measures

Our primary outcome was an injection-related hospitalisation (IRH) or death (IRD) post-SVR. We defined an injection-related cause based on ICD codes present in the primary or supplementary diagnostic position. Heroin has been and remains the predominant drug injected in Scotland (University of the West of Scotland, 2015), therefore the relevant outcome codes comprised opiate-related: *mental and behavioural disorders due to opiate misuse* (ICD-10: F11), *poisoning due to opium* (ICD-9: 965.0; ICD-10: T40.0), *poisoning due to heroin* (ICD-10: T40.1), *accidental poisoning due to heroin* (ICD-9: E8500; ICD-10: X42.4), *accidental poisoning due to opium* (ICD-10: X42.9), *intentional self-poisoning by exposure to opium* (ICD-10: X62.9), *opiate dependence* (ICD-9: 3040), *non-dependent opiate use* (ICD-9: 3055), *finding opiates in blood* (ICD-10: R781), and injection-related as defined in previous literature: *endocarditis* (ICD-9: 421.0; ICD-10: I33), *deep vein thrombosis* (ICD-9: 451, 453 ; ICD-10: I80), *cellulitis /abscesses* (ICD-9: 682; ICD-10: L02, L03) (Lloyd-Smith et al., 2008; Irish et al., 2007).

2.4 Explanatory variables

Behavioural and demographic exposure variables of interest were recorded for each patient pre-SVR and were obtained from clinical and SMR records.

Behavioural variables included presence of an acute alcohol intoxication-related hospital episode, and history of an IRH pre-SVR (using the above listed codes). Alcohol intoxication-related hospital episodes have been previously defined and include hospital episodes due to *problems related to lifestyle alcohol use* (ICD-10: Z72.1), *mental and behavioural disorders due to use of alcohol* (ICD-10: F10), *toxic effect of alcohol (ethanol, methanol, unspecified)* (ICD-9: 980.0, 980.1, 980.9; ICD-10: T51.0, T51.1, T51.9), *blood alcohol level 100-240+ / 100 ml* (ICD-9: 790.3; ICD-10: Y90.5 – Y90.9), *evidence of alcohol involvement determined by level of intent* (ICD-10: Y91), *finding of alcohol in blood* (ICD-10: R78.0), *poisoning by and exposure to alcohol* (ICD-9: E8600-02, E8609; ICD-10: X45, X65, Y15), *alcohol deterrents* (ICD-10: Y57.3), *alcohol abuse counselling and surveillance* (ICD-10: Z71.4), *non-dependent alcohol abuse* (ICD-9: 305.0).

Additional explanatory variables for each PWID included age at SVR, gender, year of SVR (date of SVR was defined as negative HCV RNA reading 24 weeks post-treatment completion), and presence of cirrhosis at treatment initiation. Age at SVR was categorised into three groups (<30,

30-44, ≥45). Year of SVR was categorised for descriptive analysis (1992-2004, 2005-2012) and kept continuous for statistical modelling. Patients who were cirrhotic at time of treatment initiation were identified by the Clinical Database based on a combination of (i) clinical examination, (ii) radiology (ultrasound, transient elastography, computed tomography, or magnetic resonance imaging), or (iii) liver biopsy, as previously described (Innes, et al., 2012).

2.5 Statistical Analyses

All statistical analyses, data storage, and manipulation were conducted using STATA version 12 (College Station, TX, USA).

2.5a Analysis of first-time opiate or injection related hospital event or death

Firstly, Kaplan Meier survival estimates were used to calculate the estimated proportion of the cohort who had a primary outcome at three years post-SVR attainment.

Secondly, we used multivariate Cox regression to determine predictors of time to first IRH or IRD post-SVR. Time at risk was calculated in person years (PY) from date of SVR attainment to first event or end of follow-up (30th June 2012). Adjusted hazard ratios (AHR) post-SVR were generated using a multivariate Cox regression analysis including all covariates irrespective of univariate association.

2.5b Analysis of multiple opiate or injection related hospital events and/or death

A multiple events Poisson regression model was used to investigate predictors of an IRH and/or IRD risk post-SVR. Time at risk was calculated from date of SVR and stopped at either death or end of follow up, but was not censored for periods spent in hospital for any admission type. Crude, unadjusted rates were measured per 100 PY of follow-up.

3. Results

3.1 Sample Characteristics (Table 1)

Table 1 displays the demographic and behavioural characteristics of the cohort with regard to our primary outcome (i.e. an injection-related hospital episode or death post-SVR). The average age at SVR was 39.6 years (standard deviation \pm 8.2 years; range 19.0-67.7 years), and the majority were male (76%). The majority of the cohort (76%) attained SVR between 2006- June 2012. A history of an IRH pre-SVR was found for 427 (37%) of the cohort, of which 222 had an IRH within three years prior to treatment initiation (relating to 19% of the entire cohort). Thirteen percent had at least one opiate or injection-related hospital episode or death during an average follow up of 4.1 years post-SVR. Mental and behavioural disorders due to opiate misuse

(ICD10: F11) was the predominant discharge diagnosis and cause of death among 149 first-time post-SVR IRH and IRD events, accounting for 61% of our outcome, followed by cellulitis/abscess (22%), and opiate dependence (7%) (Appendix Table 1).

Kaplan Meier estimates of incurring our primary outcome at three years are presented in Table 1. Estimates were calculated at three years ensuring that >50% of our cohort had at least this amount of follow-up time post-SVR. The overall estimate of injection-related hospitalisation or death at three years post-SVR was 10.59% (95%CI 8.75 – 12.79%). This proportion varied by demographic/behavioural factors and was highest among those with an IRH pre-SVR (19.24%, 95%CI 15.2% – 24.2%). The lowest estimated proportion of an IRH or IRD was observed for those who had attained SVR between 1992-2000 (2.22%, 95% CI 0.32 – 14.75%). A Kaplan Meier curve of those PWID who remain free of both an IRH and IRD over 8 years is illustrated in Figure 1.

3.2 First-time opiate or injection-related hospital episode post-SVR

The overall crude rate of our outcome post-SVR was 3.12 per 100 PY (Table 2), with the highest incidence rate noted in PWID who had an IRH pre-SVR (6.04 per 100 PY). Within the respective exposure variable groups, those aged 30 or younger at SVR had the highest incidence (3.92 per 100 PY) when compared with those aged 45 and older, along with females (3.75 per 100 PY), and those with an alcohol intoxication-related hospital episode pre-SVR (5.67 per 100 PY).

All covariates, with the exception of gender and cirrhosis, were associated with our outcome in univariate analysis (Table 2). Significant independent predictors of an IRH or IRD post-SVR identified in multivariate Cox regression include: year of SVR (AHR: 1.07, 95% CI, 1.01 – 1.14), history of alcohol intoxication-related hospital episode pre-SVR (AHR: 1.83, 95% CI 1.29 – 2.60), and history of IRH pre-SVR (AHR: 2.59, 95% CI 1.84 – 3.64). Age at SVR did not retain its significance after adjusting for covariates.

3.3 Multiple opiate and injection-related hospital episodes post-SVR

Among 1170 PWID followed from SVR attainment, we observed a total of 225 injection-related hospital episodes and 11 deaths due to an injection-related cause. Thus there were a total of 149 first-time admissions/deaths and a further 87 subsequent readmissions/deaths following first IRH; the latter 87 readmissions/deaths related to 48 PWID with up to 8 events observed per PWID (Table 3). In univariate analysis, all factors with the exception of cirrhosis at treatment initiation were associated with incidence of IRH and/or IRD post-SVR. Female gender (adjusted incidence rate ratio [AIRR]: 1.32, 95% CI 1.00 – 1.73), history of alcohol intoxication-related hospital episode pre-SVR (AIRR: 2.95, 95% CI 2.24 – 3.89), and history of

IRH pre-SVR (AIRR: 2.59, 95% CI 1.99 – 3.36) retained their significance in the multivariate model.

4. Discussion

With highly effective but costly HCV treatments on the horizon and potential demand for treatment to increase particularly among the population who injects drugs, it is essential that the behaviours which pose a risk of reinfection post-SVR are well understood. There have been few small-scale studies examining engagement in injection drug use post-HCV antiviral treatment induced SVR. These studies rely on participation, accurate self-report by PWID, and have varied in respect of recruitment setting; thus, rates of continued injection drug use ranged considerably from 33% to 100% post-SVR (Dalgard, 2005; Grebely et al., 2009). Results obtained from our study were derived from a large anonymous record-linkage exercise of routine administrative data on all PWID undergoing therapy, thereby increasing cohort size and avoiding participation bias.

This study estimated that 10.6% of the Scottish cohort of 1170 PWID (i.e. those known to have acquired their infection through injecting drug use) had been in hospital for or had died from an injection-related cause in the first three years post-SVR. This compared to a greater proportion (19%) of the cohort who had an IRH in the three years prior to treatment initiation, which is consistent with recent evidence, also from Scotland, suggesting that patients attaining SVR lead healthier lives (Innes, et al., 2015). A minority of people who actively inject drugs likely end up in hospital or die from an injection-related cause each year. For example, a survey in England recently found 13% of 1058 people who were actively injecting drugs had been admitted to hospital with an injection site infection in the last year (Hope, et al., 2008). Further, a Canadian study found that approximately 26% of active PWID, recruited through street outreach, had been admitted to hospital (for any cause) in the previous six months (Palepu et al., 1999). Given this context, it is then plausible that a greater proportion of our cohort – potentially several-fold higher than the 10.6% reported here within three years of SVR – were injecting drugs during the early years following successful therapy.

A relatively low risk of HCV reinfection post-SVR has so far been reported from studies involving PWID (pooled rate of 2 per 100 PY from recent meta-analysis), with risk of HCV reinfection greater among those reporting actively injecting drugs (6 per 100PY); however these were predominately centred in settings with considerable harm reduction and clinical support and thus may not reflect the wider injecting population (Aspinall et al., 2013). The results here show the risk of an IRH or IRD rose over time with increasing year of SVR

attainment. This likely reflects Scotland's expansion of HCV antiviral treatment among people who had ever injected drugs, having increased nine-fold between 2001-2 and 2009-10 (McDonald et al., 2014), and broadening to not just those who have injected in the distant past, but to those who have injected recently and continue to do so. The expansion of therapy in this population group was consistent with the aims of the Scottish Government's Action Plan on HCV and now also the European and Global guidelines which endorse treatment of patients with on-going drug use. Thus, our data would suggest that reinfection post-therapy may rise in Scotland, and could increase in other countries as therapy is scaled up among PWID populations.

Additional analysis considering multiple events per patient yielded similar predictors, but also highlighted a significantly increased rate among females versus males. Female gender was an independent predictor of multiple injection-related hospitalisations post-SVR, a finding corroborating previous research (Palepu et al., 2011). It is hypothesized that this significant disparity in incidence between males and females could be due to many reasons including gender-related differences in care seeking behaviour.

Individuals found to have been hospitalised for either an IRH or alcohol intoxication-related cause prior to antiviral therapy initiation, being 30% of our cohort, were at significantly increased risk of both single and multiple IRH and/or IRD post-SVR. Likewise, those younger compared to older in age, although not significant in multivariate analysis, were more likely to engage in injecting practices post-successful treatment, as indicated by an estimated 15% and 7% of those aged under 30 and over 45 years, respectively, having been in hospital or died from an injection-related cause within three years of SVR attainment. This hospitalisation data may then help target a group who are particularly prone to re-engaging with risk behaviours.

There are some limitations to our study. Using hospital records will most likely under-represent injecting frequency post-SVR. Hospitalisations represent extreme injecting outcomes (e.g. poisoning, overdose, severe injury), and thus likely underestimate the extent to which PWID are continuing to engage in injecting drugs post-successful treatment. Additionally, utilising hospital records relies on ICD codes as a measure of current-diagnosis. ICD codes indicating opiate use or injection drug use will not always necessarily indicate acute injecting episodes and could thus include historical events or non-injecting opiate abuse, both of which could have caused an overestimation of the true rate of hospitalisation for post-SVR injection drug use. Our analysis of multiple events did not exclude time spent in hospital and thus that may have weakened the strength of association with some covariates, compared to that observed in the primary analysis of first-time IRH or IRD; further follow-up is required to fully assess the extent of readmission/death in this cohort.

This study did not explore engagement in additional risk factors of HCV reinfection (e.g. tattooing, sexual practices) post-SVR, although these are unlikely to pose the same population risk as continued injecting drug use. Further, we did not consider specifically the risk of reinfection here, as it required follow-up laboratory data on HCV RNA testing, but this is now the focus of a subsequent study. This risk behaviour research has, however, informed the need to fully understand the extent of testing and diagnosis of PWID post-SVR. Additionally, SVR patients account for roughly 60% of the overall treated population, and we therefore did not report on the behaviours of remaining 40% who were treated and did not attain the optimal outcome, leaving scope for further research using such a comparison group (Innes, et al., 2012).

Implications and Recommendations

Treatment induced viral clearance is well known to improve health outcomes, yet it does not completely remove the risk of liver-related morbidity and mortality. Lifestyle factors- that can either accelerate the rate of liver disease progression (e.g. alcohol consumption) or cause re-infection pose a significant excess risk of liver disease among patients who have attained SVR (Innes, et , 2013). This study indicates that the risk of HCV reinfection post-SVR might increase as treatment is expanded and scaled up among injecting populations.

Treatment regimens that are highly effective, reduced in toxicity, and shorter in duration are at the forefront of current HCV research and care. The benefits of such treatments offer greater opportunity to scale up therapy among this population who inject drugs than ever before. Modelling studies have further illustrated the potential to reduce and control HCV transmission among PWID through such a treatment-to-prevent approach (Martin et al., 2011b, 2013). Our findings highlight that for patients who successfully complete treatment and would ordinarily be discharged from care, continued monitoring with RNA testing would be advised for those with on-going risk behaviour, in line with European guidelines (EASL, 2015). Harm reduction interventions aimed at reducing the risk of HCV transmission should also continue to be promoted once treatment ceases.

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Contributors

HV performed the data analysis and interpretation under the supervision of JL, and drafted the paper under the supervision of SH and DG. SH and DG conceived, proposed, and oversaw the

scope of the project. AW deterministically linked hospitalisation and mortality data with HCV Clinical and Diagnosis databases. All other authors provided clinical data, manuscript revisions, and approved final submission.

Conflict of interest

None declared

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References

Arain, A., Robaey, G., 2014. Eligibility of persons who inject drugs for treatment of hepatitis C virus infection. *World Journal of Gastroenterology*. 20, 12722-12733.

Aspinall, E.J., Corson, S., Doyle, J.S., Grebely, J., Hutchinson, S.J., Dore, G.J., Goldberg, D.J., Hellard, M.E., 2013. Treatment of hepatitis C virus infection among people who actively inject drugs: a systematic review and meta-analysis. *Clinical Infectious Diseases*. 57, 80-89.

Chisholm M. Members' Debate on Hepatitis C, 30th June, 2004. Edinburgh: Scottish Parliament.

Dalgard, O., 2005. Follow up studies of treatment for hepatitis C virus infection among injection drug users. *Clinical Infectious Diseases*. 2005;40:S336-8.

EASL. EASL recommendations on treatment of hepatitis C 2015 [Journal of Hepatology] Available: <http://www.easl.eu/medusa/cpg/HEPC-2015/Full-report.pdf>

Grady, B.P., Schinkel, J., Thomas, X.V., Dalgard, O., 2013. Hepatitis C reinfection following treatment among people who use drugs. *Clinical Infectious Diseases*. 57, 105-10.

Grebeley, J., Knight, E., Ngai, T., Genoway, A., Raffa, J.D., Storms, M., Gallagher, L., Krajden, M., Dore, G.J., Duncan, F., Conway, B., 2009. Reinfection with hepatitis C virus following sustained virological response in injection drug users. *Journal of Gastroenterology and Hepatology*. 25, 1281-1284.

Health Protection Agency. Hepatitis C in UK: Annual report 2013. Available from:http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317139502302

Hope, V., Kimber, J., Vickerman, P., Hickman, M., Ncube, F., 2008. Frequency, factors, and costs associated with injection site infections: Findings from a national multi-site survey of injecting drug users in England. *BMC Infectious Diseases*. 8, 120-128.

Hutchinson, S.J., Roy, K.M., Wadd, S., Bird, S.M., Taylor, A., Anderson, E., Shaw, L., Codere, G., Goldberg, D.J., 2006. Hepatitis C virus infection in Scotland: epidemiological review and public health challenges. *Scottish Medical Journal*. 2006, 8-15.

Innes, H.A., Hutchinson, S. J., Barclay, S., Cadzow, E., Dillon, J.F., Fraser, A., Goldberg, D.J., Mills, P.R., McDonald, S.A., Morris, J., Stanley, A., Hayes, P.; on behalf of the Hepatitis C Clinical Database Monitoring Committee, 2013. Quantifying the fraction of cirrhosis attributable to alcohol among chronic hepatitis C virus patients: implications for treatment cost-effectiveness. *Hepatology*. 57, 451-460

Innes, H.A., Hutchinson S.J. Allen, S., Bhattcharyya, D., Bramley, P., Carman, B., Delahooke, T.E.S., Dillon, J., Goldberg, D., Kennedy, N., Mills P., Morris, J., Morris, J., Robertson, C., Stanley, A.J., Hayes, P., the Hepatitis C Clinical Database Monitoring Committee, 2012. Ranking predictors of sustained viral response for patients with chronic hepatitis C treated with pegylated interferon and ribavirin in Scotland. *European Journal of Gastroenterology & Hepatology*. 24, 646-655

Innes, H.A., Hutchinson, S.J., Allen, S., Bhattacharyya, D., Bramley, P., Delahooke, T.E.S, Dillon, J.F., Forrest, E., Fraser, A., Gillespie, R., Goldberg, D.J., Kennedy, N., McDonald, S., McLeod, A., Milles, P.R., Morris, J., Hayes, P., 2011. Excess liver-related morbidity of chronic hepatitis C patients, who achieve a sustained viral response, and are discharged from care. *Hepatology*. 54, 1547-1558.

Innes, H.A., McDonald, S.A., Dillon, J.F., Allen, S., Hayes, P.C., Goldberg, D.G., Mills, P.R., Barclay, S.T., Wilks, D., Valerio, H., Fox, R., Bhattacharyya, D., Kennedy, N., Morris, J., Fraser, A., Stanley, A.J., Bramley, P., Hutchinson, S.J., 2015. Toward a more complete understanding of the association between a hepatitis C sustained viral response and cause-specific outcomes. *Hepatology*. doi:10.1002/hep.27766.

Irish, C., Maxwell, R., Dancox, M., Brown, P., Trotter, C., Verne, J., Shaw, M., 2007. Skin and soft tissue infection and vascular disease among drug users, England. *Emerging Infectious Diseases*. 13, 1510-1511.

Iversen, J., Maher, L., 2012. Australian NSP survey National data report 2007-2011: Prevalence of HIV, HCV and injecting and sexual behaviour among NSP attendees. Australian Syringe Programs and Harm Reductions Services in Australia, The Kirby Institute for infection and immunity.

Kendrick, S., Clarke, J., 1993. The Scottish record linkage system. *Health Bulletin (Edinburgh)*. 51, 72-79.

Lloyd-Smith, E., Wood, E., Zhang, R., Tyndall, M.W., Montaner, J.S., Kerr, T., 2008. Risk factors for developing cutaneous injection-related infection among injection drug users: a cohort study. *BMC Public Health*. 8, 405-410.

Martin, N.K., Vickerman, P., Miners, A., Foster, G.R., Hutchinson S.J., Goldberg, D.J., Hickman, M., 2011. Cost effectiveness of hepatitis C virus antiviral treatment for injection drug user populations. *Hepatology*. 000, 1-9.

Martin, N.K., Vickerman, P., Foster, G. R., Hutchinson, S.J., Goldberg, D.J., Hickman, M., 2011. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modelling analysis of its prevention utility. *Journal of Hepatology*. 54, 1137-1144.

Martin, N.K., Vickerman, P., Grebely, J., Hellard, M., Hutchinson, S.J., Lima, V.D., Foster, G.R., Dillon, J.F., Goldberg, D.J., Dore, G.J., Hickman, M., 2013. Hepatitis C virus treatment for prevention among people who inject drugs: modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology*. 58, 1598-1609.

Mathers, B.M., Degenhardt, L., Phillips, B., Wiessing, L., Hickman, M., Strathdee, S.A., Wodak, A., Panda, S., Tyndall, M., Toufik, A., Mattick, R.P., 2008. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. *Lancet*. 372, 1733-1745.

McDonald, S.A., Hutchinson, S.J., Bird, S.M., Robertson, C., Mills, P.R., Dillon, J.F., Goldberg, D.J., 2008. A record-linkage study of the development of hepatocellular carcinoma in persons with hepatitis C infection in Scotland. *British Journal of Cancer*. 99, 805-810.

McDonald, S.A., Hutchinson, S.J., Innes, H.A., Allen, S., Bramley, P., Bhattacharyya, D., Carman, W., Dillon, J.F., Fox, R., Fraser, A., Goldberg, D.J., Kennedy, N., Mills, P.R., Morris, J., Stanley, A.J., Wilks, D., Hayes, P.C., 2014. Attendance at specialist hepatitis clinics and initiation of antiviral treatment among persons chronically infected with hepatitis C: examining the early impact of Scotland's Hepatitis C Action Plan. *Journal of Viral Hepatitis*. doi:10.1111/jvh.12153.

Nelson, P.K., Mathers, B.M., Cowie, B., Hagan, H., Des Jarlais, D., Horyniak, D., Degenhardt, L., 2011. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of

Palepu, A., Strathdee, S.A., Hogg, R.S., Anis, A.H., Rae, S., Cornelisse, P.G., Patrick, D.M., O'Shaughnessy, M.V., Schechter, M.T., 1999. The social determinants of emergency department and hospital use by injection drug users in Canada. *J Urban Health*. 76, 409-18.

Palepu, A., Tyndall, M.W., Leon, H., O'Shaughnessy, M.V., Schechter, M.T., Anis, A.H., 2001. Hospital utilization and costs in a cohort of injecting drug users. *Canadian Medical Association Journal*. 165, 415-420.

Scottish Government Health Department, 2008. Hepatitis C Action Plan for Scotland: Phase II: May 2008 – March 2011. Scottish Government: Edinburgh.

University of the West of Scotland, Health Protection Scotland, Glasgow Caledonian University and the West of Scotland Specialist Virology Centre. The Needle Exchange Surveillance Initiative (NESI): Prevalence of HCV and injecting risk behaviours among people who inject drugs (PWID) attending injecting equipment provision services (IEPs) in Scotland, 2008/2009-2013/2014 University of the West of Scotland, January 2015. Available: <http://www.uws.ac.uk/research-institutes/social-sciences/health-behaviours-and-policy/needle-exchange-surveillance-initiative/>

TABLES:

Table 1. Description of cohort of 1170 PWID who attained a sustained viral response (SVR) in Scotland, 1992-2012; Kaplan Meier estimates of IRH or IRD at three years post-SVR

Table 2. Cox regression, risk of first IRH or IRD among 1170 PWID who attained SVR in Scotland, 1992-2012.

Table 3. Poisson regression, incidence and risk of multiple IRH and/or IRD among 1170 PWID who attained SVR in Scotland, 1992-2012.

Figure 1. Kaplan Meier Curve estimating the proportion of patients remaining free of an injection-related hospitalisation or death among 1170 PWID who attained SVR in Scotland, 1992-2012.

Appendix Table 1: Frequency and proportion of opiate and injection-related ICD codes identified in first-time IRH or IRD post-SVR

Characteristics	N(%)	IRH or IRD post-SVR, n (%N)	Kaplan Meier estimated proportions of opiate or injection hospital episodes/deaths at 3 years post-SVR % (95% CI)
Total	1170 (100)	149 (13)	10.59 (8.75 – 12.79)
Age at SVR			
<30	142 (12)	23(16)	13.71 (8.53 – 21.62)
30-44	738 (63)	103(14)	11.28 (8.93 – 14.21)
≥45	290 (25)	23(8)	7.19 (4.50 – 11.39)
Gender			
Male	889 (76)	104 (12)	10.26 (8.20 – 12.80)
Female	281 (24)	45 (16)	11.65 (8.07 – 16.66)
Year of SVR			
1992-2000	45 (4)	8 (18)	2.22 (0.32 – 14.75)
2001-2005	236 (20)	48 (20)	8.50 (5.57 – 12.86)
2006-2012	889 (76)	93 (10)	12.03 (9.67 – 14.93)
Cirrhosis diagnosis at treatment initiation			
No	1081 (92)	137 (13)	10.28 (8.40 – 12.56)
Yes	89 (8)	12 (13)	14.65 (8.05 – 25.73)
Alcohol intoxication-related hospital episode pre-SVR			
No	912 (78)	98 (11)	8.69 (6.84 – 11.02)
Yes	258 (22)	51 (20)	17.58 (12.81 – 23.87)
Opiate or injection-related hospital episode pre-SVR			
No	743 (63)	63 (8)	6.04 (4.38 – 8.31)
Yes	427 (37)	86 (20)	19.24 (15.22 – 24.16)

Table 1. Description of cohort of 1170 PWID who attained a sustained viral response (SVR) in Scotland, 1992-2012; Kaplan Meier estimates of IRH or IRD at three years post-SVR

Abbreviations; IRH, injection-related hospital episode; IRD, injection-related death; SVR, sustained viral response; CI, confidence interval

Covariate	PY	Unadjusted crude rate per 100 PY (95% CI)	IRH or IRD post-SVR			
			Univariate (HR, 95%CI)	p-value	Multivariate (AHR, 95% CI)	p-value
Study	4764	3.12 (2.66 – 3.67)				
Population						
Age at SVR						
<30	586	3.92 (2.61 – 5.90)	2.07 (1.17 – 3.66)	0.013	1.51 (0.83 – 2.73)	0.179
30-44	3023	3.41 (2.81 – 4.13)	1.65 (1.02 – 2.67)	0.041	1.48 (0.93 – 2.35)	0.099
≥45	1155	1.99 (1.32 – 2.99)	1.00 (Baseline)		1.00 (Baseline)	
Gender						
Male	3564	2.92 (2.41 – 3.54)	1.00 (Baseline)		1.00 (Baseline)	
Female	1200	3.75 (2.89 – 5.02)	1.29 (0.91 – 1.83)	0.155	1.28 (0.90 – 1.83)	0.164
Year of SVR			1.10 (1.03 – 1.16)	0.006	1.07 (1.01 – 1.14)	0.025
Cirrhosis diagnosis at time of treatment initiation						
No	4376	<u>3.09 (1.76 – 5.45)</u>	1.00 (Baseline)		1.00 (Baseline)	
Yes	388	<u>3.13 (2.64 – 3.70)</u>	1.05 (0.58 – 1.90)	0.876	1.03 (0.56-1.89)	0.966
Alcohol intoxication-related hospital episode pre-SVR						
No	3864	2.54 (2.08 – 3.09)	1.00 (Baseline)		1.00 (Baseline)	
Yes	900	5.67 (4.31 – 7.46)	2.17 (1.54 – 3.05)	<0.001	1.83 (1.29 – 2.60)	0.001
Opiate or injection-related hospital episode pre-SVR						
No	3342	1.88 (1.47 – 2.41)	1.00 (Baseline)		1.00 (Baseline)	
Yes	1422	6.04 (4.90 – 7.47)	3.08 (2.22 – 4.27)	<0.001	2.59 (1.84 – 3.64)	<0.001

Table 2. Cox regression; risk of first IRH or IRD among 1170 PWID who attained SVR in Scotland, 1992-2012.

Abbreviations; PY, person years; IRH, injection-related hospital episode; IRD, injection-related death, SVR, sustained viral response; HR, hazard ratio; AHR, adjusted-hazard ratio; CI, confidence interval

Covariate	N	PY	Unadjusted crude rate per 100 PY (95% CI)	IRH and/or IRD post-SVR			
				Univariate (IRR, 95%CI)	p- value	Multivariate (AIRR, 95%CI)	p-value
Study Population	236	5319	<u>4.44 (3.87 – 5.00)</u>				
Age at SVR							
<30	37	771	<u>4.79 (3.25 – 5.35)</u>	1.77 (1.13 – 2.79)	0.012	1.32 (0.83 – 2.09)	0.239
30-44	160	3456	<u>4.62 (3.91 – 5.35)</u>	1.48 (1.04 – 2.11)	0.027	1.22 (0.85 – 1.74)	0.280
≥45	39	1092	<u>3.57 (2.45 – 4.69)</u>	1.00 (Baseline)		1.00 (Baseline)	
Gender							
Male	159	3977	<u>4.00 (3.76 – 4.62)</u>	1.00 (Baseline)		1.00 (Baseline)	
Female	77	1342	<u>5.74 (4.45 – 7.02)</u>	1.48 (1.13 – 1.95)	0.005	1.32 (1.00 – 1.73)	0.048
Year of SVR				1.05 (1.01 – 1.08)	0.015	1.03 (0.99 – 1.07)	0.107
Cirrhosis diagnosis at treatment initiation							
No	213	4849	<u>4.39 (3.80 – 4.98)</u>	1.00 (Baseline)		1.00 (Baseline)	
Yes	23	470	<u>4.89 (2.89 – 6.89)</u>	1.24 (0.81 – 1.91)	0.327	1.03 (0.66 – 1.60)	0.894
Alcohol intoxication-related hospital episode pre-SVR							
No	111	4223	<u>2.62 (2.14 – 3.11)</u>	1.00 (Baseline)		1.00 (Baseline)	
Yes	125	1096	<u>11.41 (9.40 – 13.40)</u>	2.85 (2.19 – 3.71)	<0.001	2.59 (1.99 – 3.36)	<0.001
Opiate or injection related hospital episode pre-SVR							
No	88	3621	<u>2.43 (1.92 – 2.94)</u>	1.00 (Baseline)		1.00 (Baseline)	
Yes	148	1698	<u>8.71 (8.00 – 9.43)</u>	3.79 (2.89 – 4.97)	<0.001	2.95 (2.24 – 3.89)	<0.001

Table 3. Poisson regression; incidence and risk of multiple IRH and/or IRD among 1170 PWID who attained SVR in Scotland, 1992-2012.

N, Number of observed hospital episodes; PY, person years; Rate, fitted number of hospital episodes per 100 person-years; IRH, injection-related hospital episode; IRD, injection-related death; SVR, sustained viral response; IRR, incidence rate ratio; AIRR, adjusted-incidence rate ratio; CI, confidence interval

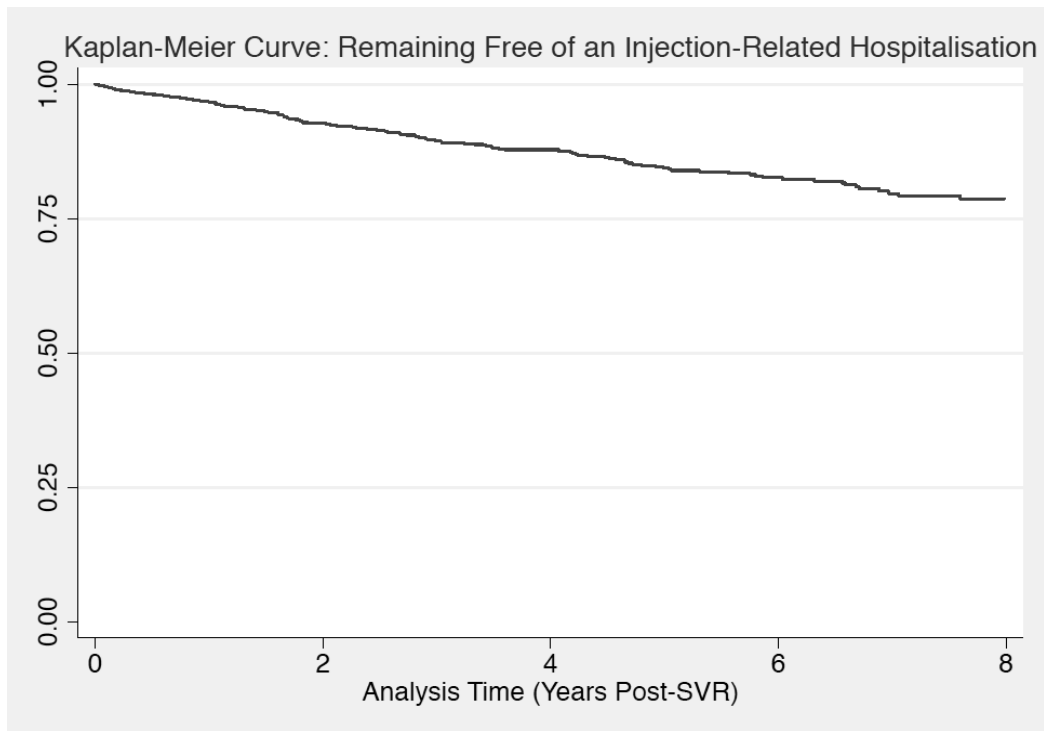


Figure1: Kaplan Meier Curve estimating the proportion of patients remaining free of in injection-related hospitalisation among 1170 PWID who attained SVR in Scotland, 1992-2012.

Code definition	ICD9/ICD10 code	Total diagnoses	Proportion first time IRH of IRD
Opiate-related			
Opiate dependence	304.0	11	7.33
Non-dependent opiate use	305.5	2	1.33
Poisoning due to opium	956.0	0	0
	T40.0	0	0
Accidental poisoning due to heroin	E8500	1	0.67
	X42.4	0	0
Mental and behavioural disorders due to heroin	F11	92	61.33
Finding opiates in blood	R78.1	0	0
Poisoning due to heroin	T40.1	7	4.67
Injection-related			
Endocarditis	421.0	1	0.67
	I33	1	0.67
Deep vein thrombosis	451	0	0
	453	0	0
	I80	2	1.33
Cellulitis/Abscesses	682	0	0
	L02	21	14.00
	L03	12	8.00

Appendix Table1: Frequency and proportion of opiate and injection-related ICD codes identified in first-time IRH or IRD post-SVR

Abbreviations: ICD, International Classification of Disease; IRH, injection-related hospital episode; IRD, injection-related death

Note: A total of six diagnostic fields are present for each one admission, therefore total frequency of ICD codes will be greater than total number of events

