The growing contribution of hepatitis C virus infection to liver-related mortality in Scotland

S A McDonald (smcdonald@nhs.net)[1], S J Hutchinson[1,2], S M Bird[2,3], C Robertson[1,2], P R Mills[4], L Graham[5], J F Dillon[6], D J Goldberg[1]
1. Health Protection Scotland, Glasgow, United Kingdom
2. Department of Mathematics and Statistics, University of Strathclyde, Glasgow, United Kingdom
3. MRC Biostatistics Unit, Institute of Public Health, Cambridge, United Kingdom
4. Gartnavel General Hospital, Glasgow, United Kingdom
5. Information Services Division, National Services Scotland, Edinburgh, United Kingdom
6. Ninewells Hospital and Medical School, Dundee, United Kingdom

The large number of individuals in Scotland who became infected with the hepatitis C virus (HCV) in the 1970s and 1980s leads us to expect liver-related morbidity and mortality to increase in the coming years. We investigated the contribution of HCV to liver-related mortality in the period January 1991 to June 2006. The study population consisted of 26,861 individuals whose death record mentioned a liver-related cause (underlying or contributing). Record-linkage to the national HCV Diagnosis database supplied HCV-diagnosed status for the study population. The proportion diagnosed with HCV among people dying from a liver-related cause rose from 2.8% (1995-1997) to 4.4% (2004-June 2006); the largest increase occurred in those aged 35-44 years at death (7% to 17%). Among all deaths from a liver-related cause, an HCV-positive diagnosis was more likely in those who died in 2001 or later than those who died in 1995-1997 (2001-2003: odds ratio=1.4, 95% confidence interval: 1.1-1.7; 2004-June 2006: 1.6, 1.3-2.0), and in those who died at under 55 compared with at least 55 years of age. HCV infection represents a significant, growing, public health burden in Scotland in terms of early deaths from liver disease.

Introduction

Mortality from severe liver disease, of which major contributing factors include excessive alcohol consumption and chronic infection with the hepatitis C virus (HCV), is increasing in Scotland [1,2] and in other developed countries, such as the United States of America [3]. About 1,500 new HCV diagnoses are made each year in Scotland (population 5.1 million in 2006) [4], and projection models of HCV-related liver disease forecast significant rises in morbidity and mortality over the coming decades, placing a growing clinical and economic burden on the Scottish healthcare system [5]. Given the large number of individuals chronically infected with HCV, and the fact that cirrhosis develops in 5%-15% of these individuals within 20 years of

infection [6] and in about 20% within 30 years [7], it is important to ascertain the contribution of chronic HCV infection to liver-related mortality.

The existence of high-quality national HCV diagnosis and mortality databases provided the opportunity to use record-linkage methods to investigate the prevalence of diagnosed HCV infection in people who died from liver disease. The goals of this study were therefore to estimate the contribution of HCV infection to liver-related deaths in Scotland and to examine trends in this contribution over time and by age group. Up-to-date information regarding the contribution of HCV to mortality from liver disease is required to inform public health intelligence and health service planning, and as a calibration check on projections.

Methods
Study population and data sources
Death registrations are held by the General Register Office for Scotland (GROS). The study population consisted of all those who died from 1 January 1991 to 30 June 2006, and whose death certificate specified a liver-related condition.

International Classification of Diseases (ICD) codes were used to extract all records from the deaths register in which a liver-related condition was listed as either the underlying cause (i.e. the disease or injury initiating the train of events leading directly to death) or a contributing cause of death (n=26,861). We obtained underlying and contributing cause-of-death codes from ICD's ninth revision (ICD-9) for deaths between 1989 and 1999 and the tenth revision (ICD-10) for deaths between 2000 and 2006. The relevant cause-of-death categories were: liver cancer, alcoholic liver disease, nonalcoholic liver disease, viral hepatitis, and sequelae of viral hepatitis (Table 1). Specific mention of viral hepatitis C (ICD-10 B17.1, B18.2), unspecified viral hepatitis C (ICD-9 070.7), or other/unspecified viral

hepatitis (ICD-9 070.4-6, 070.9) as a cause of death was also noted, to assess the frequency with which HCV is mentioned on the death certificate. Liver-related deaths among those diagnosed HCV antibody-positive (with or without mention of HCV on the death record) were determined through record-linkage between the GROS deaths registry and the HCV Diagnosis database (details below).

Carstairs social deprivation scores (coded as quintiles) were available for each death record; deprivation score is determined from postcode sector of residence and is based on 2001 census variables [8]. The highest quintile corresponds to the 20% most deprived localities.

The HCV Diagnosis database, maintained by Health Protection Scotland (HPS), is a database of all individuals who have been diagnosed HCV positive in Scotland since testing began in 1991 [9]; laboratory detection of hepatitis C antibody positivity is a requirement for inclusion. This database contains the following non-named information: surname Soundex (a consonant-only phonetic encoding), forename initial, date of birth, sex, and postcode district of residence, as well as data concerning risk activities and the date of the earliest positive specimen. The database contained records for 20,969 persons diagnosed HCV positive between 1 January 1991 and 30 June 2006 [4]. As no probabilistic linkages between the GROS deaths register and the HCV diagnosis database were achieved if the HCV diagnosis record was lacking date of birth and two or more other identifiers, records for 1,295 out of 20,969 HCV-diagnosed people (6%) were deemed to have insufficient identifiers for linkage. Of

TABLE 1

Deaths from liver-related (underlying/contributing) conditions (n=26,861), and those diagnosed hepatitis C virus-positive (n=871), by cause-of-death category, Scotland, 1 January 1991 to 30 June 2006

Underlying/contributing cause of death	n (%)	HCV[a] (%)	HCV/n %
Alcoholic liver disease (ICD-10 K70; ICD-9 571.0-571.3)	12,018 (44.7)	279 (32)	2.3
Non-alcoholic liver disease (ICD-10 K71-77; ICD-9 570, 571.4-571.9, 572-573)	17,304 (64.4)	500 (57)	2.9
Hepatocellular carcinoma (ICD-10 C22.0, ICD-9 155.0)	1,797 (6.7)	116 13)	6.5
Viral hepatitis (ICD-10 B15-19; ICD-9 070)	620 (2.3)	456 (52)	73.5
Sequelae of viral hepatitis (ICD-10 B94.2, R17, R18, I85.0, I98.2; ICD-9 789.5, 456.0)	1,811 (6.7)	85 (10)	4.7
Total	26,861 (100)	871 (100)	3.2

HCV: hepatitis C virus-positive.

[a] Number of deaths among those diagnosed HCV-positive, determined through linkage to HCV Diagnosis database.

TABLE 2

Deaths from liver-related (underlying/contributing) conditions (n=26,861), and those diagnosed HCV-positive (n=871), multifactorial logistic regression analysis, Scotland, 1 January 1991 to 30 June 2006

Factor	Level	n	HCV[a]	(%)	OR	95% CI
Sex	Female[b]	10,200	223	(2.2)		
	Male	16,661	648	(3.9)	1.70	1.45-1.99
Age at death	<25	135	8	(6)	5.47	2.63-11.39
	25-34	600	103	(17)	13.72	10.69-17.61
	35-44	2,571	274	(10.7)	7.84	6.56-9.37
	45-54	5,602	228	(4.1)	2.66	2.22-3.20
	55+[b]	17,953	258	(1.4)		
Year of death	Before 1995	4,697	51	(1.1)	0.39	0.28-0.55
	1995-1997[b]	4,657	132	(2.8)		
	1998-2000	5,519	196	(3.6)	1.23	0.98-1.55
	2001-2003	6,592	257	(3.9)	1.35	1.08-1.68
	2004-2006	5,396	235	(4.4)	1.61	1.29-2.01
Deprivation quintile	First, second[b]	6,967	147	(2.1)		
	Third	4,797	145	(3.0)	1.27	1.00-1.61
	Fourth, fifth	14,940	575	(3.8)	1.36	1.12-1.64

HCV: hepatitis C virus-positive; OR: adjusted odds ratio; 95% CI: confidence interval.

[a] Number of deaths among those diagnosed HCV-positive, determined through linkage to HCV Diagnosis database.

[b] Reference.

the records with sufficient identifiers, 68% were male, and 71% (14,018/19,674) were born between 1960 and 1979.

Linkage procedure
Linkage of records between the HCV Diagnosis database and the GROS deaths registry was carried out by the Information Services Division (a division of NHS National Services Scotland) using probabilistic record-linkage techniques [10] to determine the HCV-diagnosed status of all individuals whose cause of death included a liver-related condition. These methods allow for matches using incomplete identifiers. The linked dataset was anonymised (i.e. the only identifiers retained were, date of birth, sex and postcode district of residence) before transfer to HPS for analysis. Linkages were approved by the Privacy Advisory Committee, which oversees confidentiality issues involving data held on NHS Scotland patients.

Data analysis
Logistic regression was used to estimate the association between four epidemiological variables and diagnosed HCV status (i.e. whether or not linked to the HCV Diagnosis database). These were: sex, age at death, year of death (with 1995–1997 specified as the reference category, because HCV testing was more limited

before this period), and Carstairs social deprivation quintile. We did not analyse trends in mortality rates because the HCV Diagnosis database has expanded since its inception and people in the later stages of HCV disease may have been over-represented in its earlier years. Statistical analyses were carried out using R version 2.4.0 [11].

To estimate the extent of underreporting of HCV on the death certificate, we computed the proportion of death records that were linked to the HCV Diagnosis database, but failed to list an HCV code as either the underlying or a contributing cause of death. This analysis was also conducted separately for the year range 2000-2006, as the change in cause-of-death coding to the ICD-10 classification in 2000 overcomes the imprecision in the ICD-9 codes for HCV. The main data analysis was based on the linked data only.

Results
Overall description
Between 1 January 1991 and 30 June 2006, a total of 26,861 people died in Scotland whose death record specified a liver-related condition as the underlying or a contributing cause of death (Table 1). The majority of liver-related deaths occurred in males (62%; 16,660/26,861), and the median age at death was

TABLE 3

Deaths from a liver-related condition by period of death, mention of hepatitis C virus (HCV) in the death record, and linkage to the HCV Diagnosis database, Scotland, 1 January 1991 to 30 June 2006

Period	Mention of HCV in death record[a]	Linked to HCV Diagnosis database		Total (%)
		Yes (%)	No	
1991-1999	HCV mentioned HCV not mentioned **Total**	158 (51) 150 (49) **308**	45 12,617 **12,662**	**203 (%)**
2000-2006	HCV mentioned HCV not mentioned **Total**	292 (52) 271 (48) **563**	48 13,280 **13,328**	**340 (%)**
1991-2006	HCV mentioned HCV not mentioned **Total**	450 (52) 421 (48) **871**	93 25,897 **25,990**	**543 (%)**

HCV: hepatitis.
[a]Unlinked per cent gives the percentage of death records not linked to the HCV Diagnosis database.

TABLE 4

Numbers of deaths from liver-related conditions, proportions of those diagnosed hepatitis C virus-positive, by age at death and year of death, Scotland, 1995–1997 and January 2004–June 2006

Age at death (%)	1995-1997		1998-2000		2001-2003		2004-June 2006		Total	
	n	HCV[a] (%)	n	HCV[a] (%)	n	HCV[a] (%)	n	HCV[a] (%)	n	HCV[a] (%)
<25	32	4 (13)	29	2 (7)	17	0 (0)	17	0 (0)	**95**	**6 (6)**
25-34	107	20 (19)	143	27 (19)	138	25 (18)	117	20 (17)	**505**	**92 (18)**
35-44	432	30 (7)	544	66 (12)	691	86 (12)	478	80 (17)	**2,145**	**262 (12.2)**
45-54	972	23 (2.4)	1,196	46 (3.8)	1,444	76 (5.3)	1,180	75 (6.4)	**4,792**	**220 (4.6)**
55+	3,114	55 (1.8)	3,607	55 (1.5)	4,302	70 (1.6)	3,604	60 (1.7)	**14,627**	**240 (1.6)**
All ages	4,657	132 (2.8)	5,519	196 (3.6)	6,592	257 (3.9)	5,396	235 (4.4)	**22,164**	**820 (3.7)**

HCV: hepatitis.
[a]Numbers of deaths diagnosed HCV-positive, determined through linkage to HCV Diagnosis database.

61 years (interquartile range (IQR): 51–71) (Table 2). The overall proportion of deaths linked to the HCV Diagnosis database was 3.2% (871/26,861). The median age at death for individuals identified as diagnosed HCV-positive was 47 years (IQR: 39–58).

We report on deaths from underlying or contributing liver-related causes (n = 26,861), but note that distributions of baseline characteristics and annual trends were similar if the data were restricted to deaths from underlying liver-related causes only (n=16,767; data not shown).

Mention of HCV in death records

Viral hepatitis C was listed as the underlying or a contributing cause of death in 1.6% (543/26,861) of all liver-related deaths, and in 52% (450/871) of liver-related deaths linked to the HCV Diagnosis database. This proportion remained the same: 292/563 (52%) when liver-related deaths occurring from 2000 onwards only (n=13,891) were considered (Table 3).

Alcohol (ICD-10 K70, ICD-9 571.0-3) was mentioned in 45% (12,018/26,861) of all liver-related death records (Table 1), but in 51% of the group aged 25–34 years at death (308/600). People on the HCV Diagnosis database accounted for 17% of the liver-related deaths (17%) in the 25–34 age group (Table 2) and 69% of these deaths mentioned an alcohol-related ICD code (data not shown).

Odds of being diagnosed HCV-positive

Of those whose cause of death included a liver-related condition (either underlying or contributing), the odds of being diagnosed HCV-positive were significantly higher for males than for females, and for those who died before the age of 55 years than those who died aged 55 or older. Compared with deaths occurring 1995-1997, the odds of being HCV-diagnosed were higher for deaths occurring in 2001. People who lived in the more deprived regions had significantly higher odds of being HCV-diagnosed than people who lived in the two least deprived quintiles (Table 2). Of the HCV-diagnosed individuals, 32% (278/871) were born between 1960 and 1979. The median interval between HCV diagnosis and death was 2.1 years (range -0.4 to 14.5 years).

Table 4 compares the number and proportion of HCV-linked deaths by age at death and year of death categories, between 1995-1997 and 2004-June 2006. A trend test showed that HCV-linked deaths formed an increasing proportion of liver-related deaths over time, from 2.8% in 1995–1997 to 4.4% in 2004–June 2006 (p=0.012). The largest proportional increases over this time-span occurred in people who died aged 35-44 years (from 7% to 17%) and aged 45-54 years (from 2% to 6%). A significant difference in the rate of change in the proportion of HCV-linked deaths over time across age groups was confirmed by an interaction test (p<0.0001).

Discussion

Over the past 15 years, we have observed an increasing contribution from HCV infection to mortality due to liver-related causes in Scotland. Deaths increased steadily with time among the 35–54 years age group, and the largest percentage of deaths linked to the HCV Diagnosis database (31%) were of people born from 1950 to 1959. This is consistent with infection of young people in the 1970s and 1980s – before HCV was identified – and the natural history of chronic HCV infection [12]. HCV plays a much smaller role in liver-related deaths in older age groups mainly because relatively few individuals acquired infection at a late enough age.

A relatively high percentage of the liver-related deaths (17%) in the 25–34 age group were HCV-diagnosed individuals; the majority (69%) of these death records mentioned an alcohol-related ICD code. High liver-related mortality in this group may reflect more rapid development of liver disease associated with combined HCV infection and excessive alcohol use [13].

This study is the first to our knowledge that links national HCV diagnosis data to national mortality data to chart the contribution, over time, of HCV to all liver-related deaths [14]. Recent modelling initiatives have predicted substantial rises in HCV-related mortality in the next decade – for example, it is predicted that deaths will increase 2.8-fold between 2000 and 2020 in the United States (US) [15], and increase 1.7-fold between 2005 and 2020 (78 increasing to 129) in current/former injecting drug users (IDUs) in Scotland [16]. In this study, we observed a 1.3-fold rise in the number of liver-related deaths of people diagnosed with HCV infection (71 to 92) from 2000 to 2005, a rate which, if maintained over a further 10 years, would be even steeper than the 2005–2020 projections for IDUs in Scotland. With mortality from liver disease becoming increasingly associated with HCV infection, the importance of offering tests to individuals (particularly those under 55 years of age) presenting to hospital with an unexplained liver-related condition cannot be overemphasised.

It is notable that 48% of the records for liver-related deaths that linked to the HCV Diagnosis database did not mention HCV as either the underlying or a contributing cause of death. This finding has strong implications for public health decision making regarding the HCV epidemic. Underreporting of HCV on death certificates is a problem for many countries, such as England [17] and the US [3,18,19], undermining studies that aim to determine HCV infection's contribution to mortality from liver disease by using cause-of-death coding on death certificates.

Using record-linkage to HCV diagnosis data, we determined that 3.2% of all liver-related deaths were related to HCV infection. This proportion is substantially lower than in previous reports that have considered the role of hepatitis C in mortality from chronic liver disease

– for example, 15% (of 30,933 deaths in 1998) [18] and 16% (56/233 deaths in 2000) [19] in two studies from the US. This difference may be due to a higher prevalence of problem alcohol use in the Scottish population [20], particularly for death at a relatively young age: we note that 45% of all liver-related deaths and 69% of liver-related deaths in the 25-34 years age group mentioned one or more alcohol-related ICD codes.

Our study has important strengths and limitations. The use of a national deaths register to identify liver-related deaths has provided considerable statistical precision. The main limitations relate to a lack of information about chronic, versus resolved, infection on the HCV Diagnosis database, and to record-linkage errors. We assumed that all individuals who died from a liver-related cause and were diagnosed with HCV were chronically infected. Given that about 26% of those ever diagnosed antibody-positive appear to achieve spontaneous viral clearance [21], we may have overestimated the proportion of liver-related deaths associated with chronic HCV infection, although this is likely to be offset by underestimation due to unrecovered linkages – for example, if critical identifiers were erroneous or missing.

A larger problem of underestimation exists because 60% to 70% of the chronically HCV-infected population in Scotland are estimated to remain undiagnosed [12]. Because these 'missing' HCV-related deaths have not been added to the known HCV-related deaths reported here, we have quantified only the lower bound of the true contribution of HCV infection to liver-related mortality. It is likely, however, that more than 60%-70% of people with HCV infection presenting with fatal liver disease will be tested and diagnosed. Related to this issue, we note that if, say, postmortem HCV testing increased over the study period this would account for part of the increasing trend in the proportion of HCV-diagnosed liver-related deaths. Similarly, if the majority of the 6% of HCV Diagnosis records that were excluded from analysis (because of insufficient identifiers) were from the early part of the database period, then the increasing trend observed in the proportion of deaths that were HCV-diagnosed might be overestimated. No indication of such a distribution was found, however.

Because injecting drugs is the commonest risk factor for acquiring HCV infection in Scotland, the adjusted odds ratios reported here for sex and social deprivation are partly capturing differences in IDU prevalence: a higher proportion of males than females are IDUs, and IDU prevalence is greatest for people who live in the most deprived areas [22].

As we lacked data regarding problem alcohol use, we have not been able to estimate the relative contributions of HCV infection and alcohol consumption to liver-related mortality in people diagnosed with HCV infection; this is of particular interest for cases in whom alcoholic liver disease was specified as the underlying cause of death. High levels of alcohol consumption have been implicated as contributing to premature death in people with chronic HCV infection [23], consistent with a synergistic effect of alcohol and chronic HCV infection on the development of liver disease [13]. IDUs – who comprise the majority of the chronically-infected HCV population in Scotland – have been reported to have a relatively high prevalence (37%–53%) of heavy alcohol consumption (defined as a score of eight or more on the Alcohol Use Disorders Identification Test [AUDIT] scale [24,25], or as two positive responses in the CAGE questionnaire [26]). Consequently, the increase over time in the proportion of liver-related deaths linked to the HCV Diagnosis database that we observed may be partly attributed to a rise in problem alcohol use, if alcohol consumption has increased in the HCV-diagnosed population over the study period.

In conclusion, HCV infection constitutes a significant, growing, public health burden in Scotland in terms of mortality from liver disease. Mortality from HCV-related liver disease is anticipated to increase as the population infected in the 1970s and 80s ages, those infected in the 1990s enter their second or third decade after HCV infection, and the size of the chronically-infected population grows. A better understanding of the risk factors associated with developing HCV-related liver disease will improve treatment and survival.

References

1. Leon DA, McCambridge J. Liver cirrhosis mortality rates in Britain from 1950 to 2002: an analysis of routine data. Lancet. 2006;367(9504):52-6.
2. Palmateer N, Hutchinson S, McLeod A, Codere G, Goldberg D. Comparison of deaths related to hepatitis C and AIDS in Scotland. J Viral Hepat. 2007;14(12):870-4.
3. Wise M, Bialek S, Finelli L, Bell B, Sorvillo F. Changing trends in hepatitis C-related mortality in the United States; 1995-2004. Hepatology. 2008;47(4):1128-35.
4. Health Protection Scotland (HPS). Surveillance of known hepatitis C antibody positive cases in Scotland: results to 30 June 2006. HPS Weekly Report. 2006;40(2006/38):202-6.
5. Hutchinson S, Bird S, Goldberg D. Modeling the current and future disease burden of hepatitis C among injection drug users in Scotland. Hepatology. 2005;42(3):711-23.

6. Freeman A, Dore G, Law M, Thorpe M, von Overbeck J, Lloyd A, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatology. 2001;34(4 Pt 1):809-16.

7. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008;48(2):418-31.

8. Carstairs V, Morris R. Deprivation and health in Scotland. Health Bulletin. 1990;48(4):162-75.

9. Shaw L, Taylor A, Roy K, Cameron S, Burns S, Molyneaux P, et al. Establishment of a database of diagnosed HCV-infected persons in Scotland. Commun Dis Public Health. 2003;6(4):305-10.

10. Kendrick S, Clarke J. The Scottish Record Linkage System. Health Bull (Edinb). 1993;51:72-9.

11. R Development Core Team. R: a language and environment for statistical computing. Vienna; Austria: R Foundation for Statistical Computing; 2006.

12. Hutchinson S, Roy K, Wadd S, Bird S, Taylor A, Anderson E, et al. Hepatitis C virus infection in Scotland: epidemiological review and public health challenges. Scott Med J. 2006;51(2):8-15.

13. Hutchinson S, Bird S, Goldberg D. Influence of alcohol on the progression of hepatitis C virus infection: a meta-analysis. Clinical Gastroenterology and Hepatology. 2005;3(11):1150-9.

14. Bird S, Goldberg D, Hutchinson S. Projecting severe sequelae of injection-related hepatitis C virus epidemic in the UK. Part 1: Critical hepatitis C and injector data. J of Epidemiology and Biostatistics;2001(6):3.

15. Davis G, Albright J, Cook S, Rosenberg D. Projecting future complications of chronic hepatitis C in the United States. Liver Transpl. 2003;9(4):331-8.

16. Hutchinson S, Bird S, Goldberg D. Review of models used to predict the future numbers of individuals with severe hepatitis C disease: therapeutic and cost implications. Expert Review of Pharmacoeconomics and Outcomes Research. 2006;6(6):627-39.

17. Mann AG, Ramsay ME, Brant LJ, Balogun MA, Costella A, Harris HE. Diagnoses of, and deaths from, severe liver disease due to hepatitis C in England between 2000 and 2005 estimated using multiple data sources. Epidemiol Infect. 2009;137(4):513-8.

18. Vong S, Bell B. Chronic liver disease mortality in the United States; 1990-1998. Hepatology. 2004;39(2):476-83.

19. Manos MM, Leyden WA, Murphy RC, Terrault NA, Bell BP. Limitations of conventionally derived chronic liver disease mortality rates: Results of a comprehensive assessment. Hepatology. 2008;47(4):1150-7.

20. Information Services Division (ISD). Alcohol Statistics Scotland. Edinburgh: ISD; 2007.

21. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat. 2006;13(1):34-41.

22. Hay G, Gannon M, McKeganey N, Hutchinson S, Goldberg D. Estimating the national and local prevalence of problem drug misuse in Scotland: executive report. Edinburgh: ISD; 2005.

23. Chen C, Yoon Y, Yi H, Lucas D. Alcohol and hepatitis C mortality among males and females in the United States: a life table analysis. Alcohol Clin Exp Res. 2007;31(2):285-92.

24. Campbell J, Hagan H, Latka M, Garfein R, Golub E, Coady M, et al. High prevalence of alcohol use among hepatitis C virus antibody positive injection drug users in three US cities. Drug Alcohol Depend. 2006;81(3):259-65.

25. Watson B, Conigrave K, Wallace C, Whitfield J, Wurst F, Haber P. Hazardous alcohol consumption and other barriers to antiviral treatment among hepatitis C positive people receiving opioid maintenance treatment. Drug Alcohol Rev. 2007;26(3):231-9.

26. Graham L. Prison health in Scotland: a health-care needs assessment. Scottish Prison Service; 2007