Modeling the Current and Future Disease Burden of Hepatitis C Among Injection Drug Users in Scotland

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Quantitative estimates of the current and future burden of hepatitis C virus (HCV) disease are required to plan a public health response to the HCV epidemic with regard to both prevention and treatment. A forward projection model was used to estimate the numbers of both current and former injecting drug users (IDUs) who acquired HCV and progressed to moderate and severe disease in Glasgow and Scotland during 1960-2030. The model was designed to synthesize information on the incidence and cessation of injecting drug use, the incidence of HCV infection among IDUs, the rate of HCV disease progression, and the annual number of IDUs developing HCV-related decompensated cirrhosis. During 2003, a total of 17,400 and 42,900 HCV-infected IDUs were estimated in Glasgow and Scotland, respectively; this compares with approximately 5,000 and 13,900 diagnosed, respectively, and 13,200 and 32,200 with chronic HCV, respectively. The number of IDUs developing HCV-related decompensated cirrhosis in Scotland is estimated to double between 2000 and 2020. As many as 16% and 27% of former IDUs in 2005 aged 30-39 and 40-49 years, respectively, were estimated to have moderate disease, which highlights the potential benefit of targeting HCV testing at former IDUs who belong to these age groups. In conclusion, the identification and treatment of a larger proportion of former IDUs with HCV disease and education about the importance of minimal alcohol consumption are needed to help achieve a greater impact on the future morbidity and mortality of this disease. (HEPATOLOGY 2005;42: 711-723.)

In most resource-rich countries, a significant number of persons acquired hepatitis C virus (HCV) infection in the 1970s and 1980s,[1] before the identification of the virus and the availability of diagnostic tests. Chronic HCV does not result in major morbidity for many years: 4%-10% develop cirrhosis after 20 years of infection.[2] Thus, the impact of this infection on health care systems is only now becoming apparent.[3] There are also concerns about the burgeoning medical costs of treating chronic HCV. In the UK, antiviral treatment is recommended and deemed cost-effective for patients shown to have moderate HCV disease.[4,5]

In Scotland, 18,109 persons had been diagnosed with HCV by 2003[6]; among those for whom risk factor information was available, 90% had injected drugs. Less than 10% of HCV-diagnosed persons in Scotland had, however, received antiviral therapy, and 60%-80% of the total HCV-infected population likely remained undiagnosed.[7] To plan a public health response to this epidemic with regard to treatment needs and preventive measures, quantitative estimates of the current and future burden of HCV disease are required.

Our aim was to develop a model to estimate the numbers of (current and former) injecting drug users (IDUs) in Greater Glasgow and Scotland belonging to different stages of HCV disease now and in the future. Modeling was confined to the IDU population, because the overwhelming majority of HCV transmissions in Scotland have been associated with this group. To determine the benefit of treating HCV-infected (former) IDUs, the impact of different antiviral treatment strategies on the incidence of severe HCV disease was explored.

Patients and Methods

Overview

The study involved three stages: (1) the development of an HCV projection model for IDUs in Greater Glas-
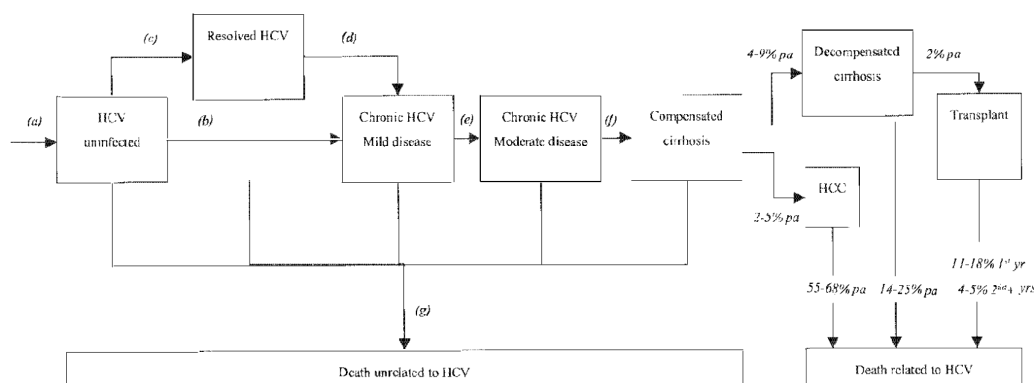
Fig. 1. Schematic outline of HCV disease stages through which current and former IDUs progress in a model according to defined transition rates. (a) Estimates of the number of individuals commencing (and ceasing) injecting drug use each year in Glasgow are shown in Appendix A. (b) Estimates of the percentage of uninfected current IDUs who acquired chronic HCV, (c) uninfected current IDUs who acquired HCV but resolved their infection, and (d) previously infected current IDUs who had resolved their infection but were reinfected and acquired chronic HCV were generated through a separate modeling exercise each calendar year in Glasgow. Of note, 15% to 40% of individuals with acute HCV were assumed to resolve their infection and become susceptible to reinfection. (e) An estimated 56% (95% CI 43%-70%) of chronically infected cases had moderate disease (defined as 3-5/6 on fibrosis and/or >3/18 on necroinflammatory scores) after 20 years of infection. (f) Progression from chronic HCV to compensated cirrhosis was modeled based on a Weibull distribution with cirrhosis prevalence estimated at 7.5% (95% CI 5%-10%) and 20% (95% CI 10%-40%) after 20 and 40 years, respectively; increased rates of progression among those who were male, older at HCV acquisition, HIV-coinfected, and heavy alcohol users were explored in the model (see Patients and Methods). (g) Annual mortality (from causes unrelated to HCV) among current IDUs was estimated in the range of 1% to 2% and among former IDUs was assumed to be two to five times higher than the age- and sex-specific rates for the general Scottish population; mortality from HIV was also accounted for in the model (see Patients and Methods). See Appendix B for further details of transition rates following the development of compensated cirrhosis. HCV, hepatitis C virus; pa, per annum; HCC, hepatocellular carcinoma.

gow (a region with approximately one third of all IDUs in Scotland[8] and a wealth of epidemiological data); (2) a comparison of the impact of different antiviral treatment scenarios on severe HCV disease; and (3) the extension of stage 1 to the entire Scottish IDU population.

The projection model was designed to incorporate the knowledge and uncertainty about major parameters relating to: (1) the IDU population (i.e., incidence and cessation of injecting and mortality); (2) the characteristics of IDUs affecting HCV disease progression (i.e., sex, age, HIV coinfection, and heavy alcohol intake); (3) the incidence of HCV infection among current IDUs; and (4) the rate of HCV disease progression (including the influence of host factors and the current uptake of antiviral therapy). Local data were used to inform the first three parameters, available up to 2000 (estimates from this year were applied in subsequent years, 2001-2030), and the worldwide literature was reviewed to inform on the fourth parameter. Modeled outcomes were fitted to data on the prevalence of current IDUs, the prevalence of HCV among current IDUs, and the incidence of decompensated cirrhosis among HCV-infected IDUs.

Model Structure

In annual cycles during 1960-2030, Markov modeling was used to simulate individuals' progression from com-

mencement of injecting drug use through predefined HCV disease states until death from causes related and unrelated to HCV (Fig. 1). Progression from one state to another was based on transition probabilities derived from a comprehensive review of the literature. The model distinguishes between HCV uninfected, chronically infected, and previously but no longer infected persons. Once chronically infected, cases had the potential to progress sequentially to moderate disease, compensated cirrhosis, and then either decompensated cirrhosis or hepatocellular carcinoma (HCC). Persons were further characterized according to age, sex, heavy alcohol use, and HIV coinfection to explore the influence of these factors on HCV disease progression. By tracking individuals' development of HCV-related complications each year, the model estimates past, current, and future HCV-related morbidity and mortality. SPLUS software (MathSoft, Inc., Seattle, WA) was used to generate simulations.

Model Parameters

The IDU Population. Estimates of the incidence and cessation of injecting during 1960-2000 in Glasgow (Appendix A) were derived previously through the use of a modified Delphi approach, which combined expert opinion with capture–recapture IDU prevalence estimates,[9] and an annual rate of mortality, from overdose and other

causes (unrelated to HCV and HIV), among current IDUs of 1%-2%.[10] Current IDUs were assumed to have ceased injecting by 50 years of age. The mortality of former IDUs from causes unrelated to HCV and HIV was assumed to be 2 to 5 times higher[11,12] than the average annual age- and sex-specific rates for the general Scottish population.

Characteristics of IDUs Affecting HCV Disease Progression. *Sex and age.* The sex and age distributions of newly initiated IDUs were based on those of IDUs surveyed in Glasgow during the 1990s[13]: 27.5% were female, and the mean age at commencement of injecting was 17.5 years up until the mid-1980s, increasing linearly thereafter to 23.5 years by 2000.

HIV coinfection. The majority of HIV infections among Scottish IDUs occurred during 1983-1985 (an estimated 1,000, 15% of whom resided in Greater Glasgow[14]). Mortality among HIV-infected IDUs was based on data generated by the Collaborative Group on AIDS Incubation and HIV Survival,[15] and adjusted down (by 75%) after 1995 to allow for increased survival due to highly active anti-retroviral therapy.

Heavy alcohol use. Studies of drug users have reported prevalences in the range of 15%-45% for either problem drinking or drinking above the recommended safe limits.[16,17] To accommodate this range of uncertainty, two rates (20% and 40%) of heavy alcohol use were explored in the model.

The Incidence of HCV Infection Among Current IDUs. Previously, estimates of the percentage of (1) uninfected current IDUs who acquired chronic HCV, (2) uninfected current IDUs who acquired HCV but spontaneously cleared their infection, and (3) previously infected current IDUs (who had cleared their infection) who were reinfected and acquired chronic HCV were generated each calendar year during 1960-2000 in Glasgow.[9] Briefly, stochastic simulation had been used to model the transmission of HCV among IDUs in Glasgow according to their needle/syringe sharing behaviors; of note, 15%-40% of those with acute HCV were assumed to recover from their infection and become susceptible to reinfection but were half as likely to develop new viremia following re-exposure.[18-20] Estimates that provided modeled HCV prevalences consistent with survey data[21] were used in the projection model.

The Rate of HCV Disease Progression. *Chronic HCV to moderate disease and compensated cirrhosis.* Progression from chronic HCV to compensated cirrhosis was modeled based on a Weibull distribution with cirrhosis prevalence estimated initially (and assessed in model fitting) at 6.5% (95% CI 3.5%-9.5%) and 20% (95% CI 10%-40%) after 20 and 40 years, respectively, according

to a systematic review of nine community-based studies.[2,22] Progression to moderate disease (defined as 3-5/6 on fibrosis and/or >3/18 on necroinflammatory scores[23]) was similarly derived from three of the community-based studies with relevant data[24-26]: an estimated 56% (43%-70%) of chronic cases had moderate disease after 20 years.

An increased rate of progression to cirrhosis among chronically HCV-infected individuals who were male (relative risk 1.6; 95% CI 1.2-2.0),[27] older at HCV acquisition (1.08 per year; 95% CI 1.04-1.12)[8], HIV coinfected (2.9; 95% CI 1.7-5.0),[28] and heavy alcohol users (2.3; 95% CI 1.7-3.3)[27] was also explored in the model.

Compensated cirrhosis to decompensated cirrhosis, HCC, and death. The transition rates following compensated cirrhosis are summarized in Fig. 1 (details in Appendix B).

Current uptake of antiviral therapy. The model was designed to take account of former IDUs' (with moderate HCV disease) initiation on, and response to, antiviral therapy. Other factors influencing eligibility for treatment (*e.g.*, heavy alcohol use and psychiatric status) were not considered. Clearance of the virus was estimated at 20%, 40%, and 50% with interferon alone, interferon plus ribavirin, and pegylated interferon plus ribavirin, respectively.[29-31] Compliance to HCV treatment once initiated was assumed to be 90%.[32,33] The number of IDUs who had been initiated on antiviral therapy in Glasgow and Scotland by the end of 2003 was estimated, optimistically, at 500 and 1,500, respectively. Uptake of treatment in subsequent years was set the same as in 2003; different uptake rates were also applied to assess the potential of antiviral therapy to reduce the incidence of severe HCV disease in the future (described below).

Model Fitting

The aim of the model fitting was to assess the validity of model assumptions to generate outcomes consistent with available epidemiological data. Each simulation generated estimates of the number of new decompensated cirrhosis cases per year (S_i) and were compared with the expected number (R_i), which were determined through record-linkage of Scotland's HCV diagnoses database with hospital records, for 1996-2001 (Fig. 2) using a standard χ^2 goodness-of-fit measure. The expected numbers of IDUs developing decompensated cirrhosis (R_i) were based on the number of HCV-diagnosed individuals admitted to the hospital with this complication, adjusted to account for the proportion estimated to be IDUs (88%), and estimated rates of nonhospitalization (14%) and non–HCV diagnosis (18%) of decompensated cases. If the goodness-of-fit test statistic $(\Sigma_{i-1996}^{2001} (S_i - R_i)^2 / R_i)$ was less than the 99.9% critical value for the χ^2 distribution on
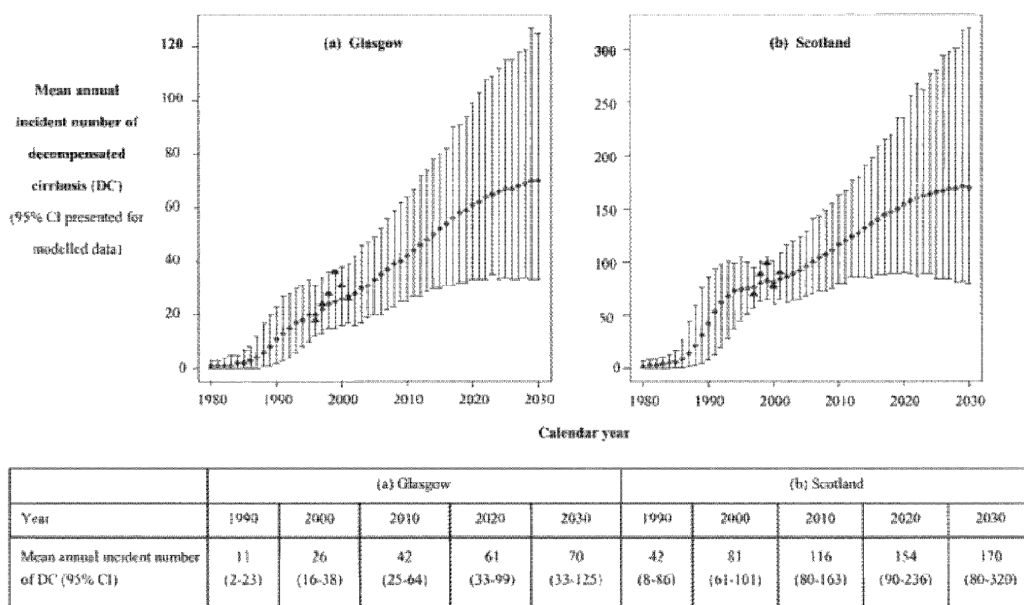
	(a) Glasgow					(b) Scotland				
Year	1990	2000	2010	2020	2030	1990	2000	2010	2020	2030
Mean annual incident number of DC (95% CI)	11 (2-23)	26 (16-38)	42 (25-64)	61 (33-99)	70 (33-125)	42 (8-86)	81 (61-101)	116 (80-163)	154 (90-236)	170 (80-320)

Fig. 2. The expected (▲) and modeled (♦) annual incident number of decompensated cirrhosis cases among HCV chronically infected IDUs in (A) Glasgow and (B) Scotland, 1980-2030 (95% CI is presented for modeled data). Models included the influence of increased progression for males, older age at HCV acquisition, coinfection with HIV, and heavy alcohol use (40% uptake). DC, decompensated cirrhosis.

five degrees of freedom, the simulated data were regarded as consistent with the record-linkage data. Simulations were performed until 1,000 accumulated, which produced simulated results consistent with record-linkage data via this criterion. The parameter values—for key uncertainties, (1) the incidence of HCV infection, (2) HCV disease progression rates (including/excluding the influence of host factors), (3) uptake of heavy alcohol use, and (4) mortality of former IDUs—that produced consistent simulation results were compared with those applied *a priori* to determine the range of model assumptions that generated the best-fitting data.

Different Antiviral Treatment Scenarios

The number of former IDUs initiated on antiviral therapy in Glasgow in 2005, and in each year thereafter, was increased from the estimated current uptake of 75 to a maximum range of 250, 500, and 1,000 per year. The stage at which former IDUs were initiated on treatment was varied between moderate disease only, a combination of moderate disease and compensated cirrhosis, and a combination of mild and moderate disease. The response to therapy was assumed to be the same irrespective of the stage of HCV disease, but was varied between the current rate of 45% (50% clearance × 90% compliance) and two improved rates of 75% and 100%. The percentage of

severe HCV-related events (*i.e.*, decompensated cirrhosis and HCC) potentially prevented among IDUs in Glasgow was estimated as a result of these different treatment scenarios.

Extension of Model to the Entire Scottish IDU Population

The model was adapted to the whole of Scotland, based on available epidemiological data, by adjusting four key parameters. First, the number of individuals who commenced injecting each calendar year was increased (twofold compared with that used for Glasgow by 1980, increasing to threefold by 1990 and fourfold by the mid-1990s) in accordance with IDU prevalence estimates for Scotland.[8,34] Second, the percentage of current IDUs who acquired HCV each calendar year was halved for Scotland compared with that for Glasgow from 1987 onward, in accordance with HCV prevalence data among current IDUs.[34,35] Third, 1,400 current IDUs were infected with HIV in Scotland during 1983-2000 (described previously). Finally, 1,500 former IDUs with moderate HCV disease in Scotland were assumed to have been initiated on antiviral therapy by the end of 2003 (described previously). All other parameters on cessation of injecting, characteristics of IDUs, HCV disease progression, and mortality rates were retained the same as in Glasgow. The

model for Scotland was similarly fitted to record-linkage data on the estimated incidence of decompensated cirrhosis among HCV-infected IDUs.

Results

Assessment of HCV Projection Model

The model, which excluded the influence of covariates (i.e., sex, age, HIV, and alcohol) on HCV disease progression, underestimated the incidence of decompensated cirrhosis among Glasgow IDUs during 1996-2001 (mean total of 72 modeled compared with 158 estimated through record-linkage); only 9% of simulations were consistent with record-linkage data. Model consistency improved to 27% and 40% following the inclusion of covariate effects with rates of heavy alcohol use at 20% and 40%, respectively. Increasing the overall progression to cirrhosis at 20 years to 7.5% (95% CI 5%-10%) generated higher consistency still: 53% in the Glasgow model with covariate effects and 40% uptake of heavy alcohol use, and 27% with the equivalent model for Scotland. The distributions for other model parameters produced by consistent simulations were not significantly different from those employed a priori. Consistent simulations from the model that assumed 7.5% (5%-10%) and 20% (10%-40%) progression to cirrhosis after 20 and 40 years, respectively, were used to generate outcomes thereafter.

Comparison of Modeled and Available Epidemiological Data

Prevalent Number of Current IDUs. The modeled prevalent numbers of current IDUs in Glasgow (mean and 95% CI for years 1990 and 2000: 8,400, 7,500-9,700; and 7,000, 6,200-8,400, respectively) and Scotland (22,200, 18,700-26,700; and 26,000, 19,000-37,200, respectively) were consistent with estimates generated mainly through capture–recapture studies (Glasgow 1990 and 2000: 8494, 95% CI 7,490-9,720[36]; and 7187, 95% CI 6,085-8,615,[34] respectively; Scotland 1990 and 2000: 21,700[8] and 25,140,[31,37] respectively).

Annual Number of Drug-Related Deaths. The modeled mean annual number of deaths among current IDUs unrelated to HCV and HIV was in the range of 100-110 (limits of 95% CIs: 70-160) for Glasgow and 350-390 (limits of 95% CIs: 220-640) for Scotland between 1999 and 2002. Assuming that 90% of these deaths were drug-related,[38] these ranges compare reasonably with the annual number of drug-related deaths reported by the Scottish General Register Office during this period for Glasgow (96-126) and Scotland (291-382).[39]

Prevalence of HCV Among Current IDUs. The modeled prevalences of HCV among current IDUs in Glasgow (mean and 95% CI for years 1990 and 2000:

71%, 62%-81%; and 62%, 53%-73%, respectively) and Scotland (58%, 46%-67%; and 45%, 38%-52%, respectively) were in accordance with survey data (Glasgow 1990-1991 and 2000: 74%, 95% CI 67%-82%[21]; 62%, 58%-66%,[35] respectively; and Scotland 2000: 44%, 30%-54%[34]).

Incidence of HCV-Related Decompensated Cirrhosis. The number of HCV-infected IDUs developing decompensated cirrhosis each year was estimated to double approximately between 2000 and 2020 in Glasgow and Scotland (Fig. 2). During 1990-1995 and 1996-2001, 15%-23% and 7%-12%, respectively, of HCV-related decompensated cases in Scotland were estimated to be HIV-coinfected (compared with 5%-10% and 2%-4%, respectively, in Glasgow), which contributed to the sharp rise in cases during the earlier period.

Modeled HCV Disease Burden

Figure 3 illustrates the rise in the mean prevalent number of HCV-infected ever IDUs in Glasgow and Scotland from only 1,700 and 3,800 in 1980 to 15,700 and 37,800 in 2000, respectively. In 2000, a mean of 12,100 and 28,700 ever IDUs in Glasgow and Scotland, respectively, were estimated to have chronic HCV; 8,700 and 19,900 of these were former IDUs, respectively (Appendix C). In Glasgow, the mean number of former IDUs with moderate HCV disease was estimated to increase 2.5-, 3.7-, and 4.1-fold between 2000 (2,100) and 2010 (5,200), 2020 (7,800), and 2030 (8,600), respectively; the mean number of ever IDUs with cirrhosis was estimated to rise 1.6-, 2.4-, and 2.6-fold between 2000 (500) and 2010 (800), 2020 (1,200), and 2030 (1,300), respectively.

Modeled Stage of HCV Disease by Age

Figure 4 illustrates the increasing severity of HCV disease with age among current and former Glasgow IDUs in 2005. The mean prevalence of cirrhosis among former IDUs increased from 0% to 27% among those under 30 and 60 years of age or more, respectively. Of relevance with regard to targeting HCV treatment, the mean estimated prevalence of moderate disease in 2005 was 16% and 27% among former IDUs aged 30-39 and 40-49 years, respectively.

Modeled Impact of Different Treatment Scenarios on Severe HCV Disease

During 2006-2030, 1,690 HCV-infected IDUs in Glasgow (who had not reached cirrhosis by 2005) were estimated to develop severe HCV disease (consisting of 1,130 and 560 cases of decompensated cirrhosis and HCC, respectively), with no uptake of antiviral therapy. Table 1 shows the percentage of severe disease that could be prevented through a range of antiviral treatment strat-
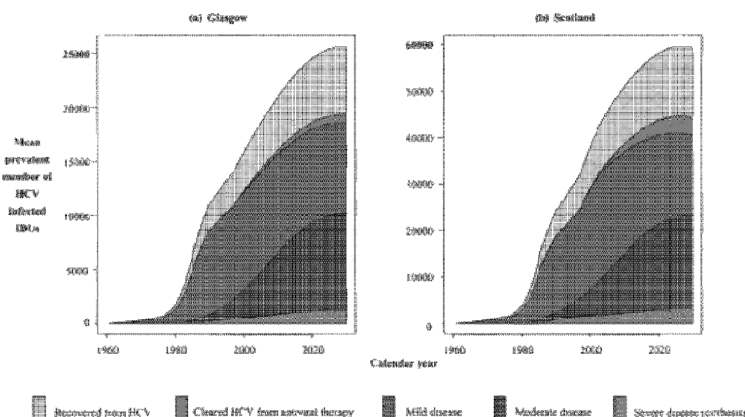
Fig. 3. The modeled prevalent number of HCV-infected IDUs in (a) Glasgow and (b) Scotland according to stage of HCV disease, 1960-2030. HCV, hepatitis C virus; IDUs, injecting drug users.

egies. Only 5% of severe disease will likely be prevented over the next 25 years with the current uptake of—and response to—therapy by 75 former IDUs (with moderate HCV disease) in Glasgow per year. Increasing the number initiated on antiviral therapy from 75 to a maximum of 250, 500, and 1,000 persons per year was estimated to prevent a further 10%, 23%, and 33% of severe disease, respectively. Treatment with more effective antiviral therapies than currently available would prevent a greater proportion of severe disease. A greater and lesser proportion of severe disease would be prevented if former IDUs with compensated cirrhosis and mild disease, respectively, had the same opportunity to be initiated on—and respond as well to—antiviral therapy as those with moderate disease.

Discussion

This is the first attempt to estimate the current and future burden of HCV disease in Scotland related to injecting drug use—data that will aid the planning of a public health response to this epidemic. A mean of 17,400 and 42,900 persons who had ever injected drugs were estimated to be living with HCV during 2003 in Glasgow and Scotland, respectively. This compares with approximately 5,000 (29%) and 13,900 (32%) diagnosed, respectively[6]—observations that are consistent with our understanding that 60%-80% of the HCV-infected population remain undiagnosed.[7] Of these infected IDUs in Glasgow and Scotland, 13,200 and 32,200 were estimated to have chronic HCV and therefore at risk of developing cirrhosis. In Glasgow and Scotland, respectively, it was further estimated that 210 and 750 HCV-infected IDUs had died prematurely from liver failure by the end of 2003, mainly over the last decade; this compares with 38 and 352 IDUs known to have died from AIDS in Glasgow and Scotland, respectively (personal communication: Glenn Codere, Health Protection Scotland).

It is estimated that the number of HCV-infected IDUs developing decompensated cirrhosis in Scotland will double between 2000 and 2020. Modeling efforts in other countries have predicted similar rises: it is estimated that mortality from HCV-related liver disease will increase twofold between 2000 and 2020 in the United States,[40] 2.5-fold between 1990 and 2020 in France,[41] and 1.9-fold between 1998 and 2020 in Switzerland.[42] The esti-
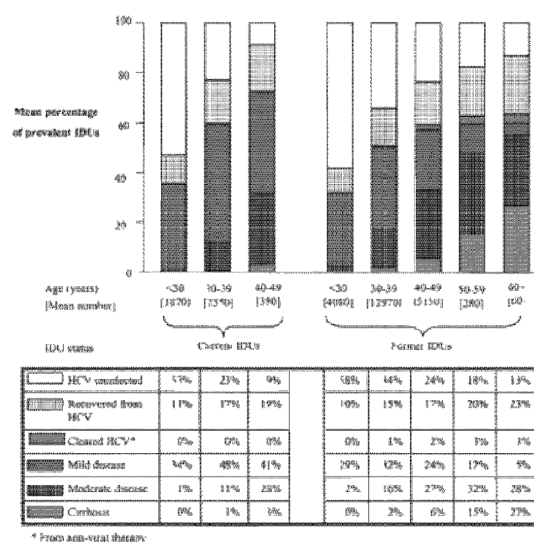

Fig. 4. The modeled prevalent number of IDUs in Glasgow in 2005 according to stage of HCV disease, current age, and IDU status.

Table 1. Modeled Mean Percentage (and 95% CI) of Severe HCV-Related Events (Total of 1,690; 95% CI 890–2,770) Potentially Prevented by Antiviral Therapy Among IDUs in Glasgow During 2006–2030 (Among Those Who Developed Cirrhosis After 2005)

Stage at Which Former IDUs Were Initiated on Treatment	Uptake of Antiviral Therapy: Maximum Number of Former IDUs Initiated per Year (Mean Total During 2005–2030)	Modelled Mean % (95% CI) of Severe Disease Prevented Among Glasgow IDUs During 2006–2030 by Treatment According to These Response Rates to Antiviral Therapy		
		45% Response	75% Response	100% Response
Mild and moderate disease	75 (1,950)	3% (2%–4%)	5% (3%–6%)	6% (4%–8%)
	250 (6,500)	9% (7%–11%)	15% (11%–19%)	20% (15%–25%)
	500 (12,990)	17% (13%–22%)	29% (22%–36%)	38% (30%–48%)
	1,000 (21,060)	30% (25%–34%)	50% (43%–56%)	67% (57%–75%)
Moderate disease	75 (1,950)	5% (3%–6%)	8% (5%–10%)	10% (7%–13%)
	250 (6,500)	15% (11%–19%)	25% (19%–32%)	33% (25%–42%)
	500 (12,750)	28% (22%–34%)	47% (37%–57%)	63% (49%–76%)
	1,000 (15,330)	38% (34%–41%)	63% (57%–67%)	84% (76%–88%)
Moderate disease and compensated cirrhosis	75 (1,950)	6% (4%–8%)	10% (7%–13%)	13% (10%–17%)
	250 (6,500)	19% (15%–24%)	32% (25%–40%)	43% (33%–53%)
	500 (12,890)	35% (28%–40%)	58% (47%–66%)	77% (63%–87%)
	1,000 (16,120)	42% (39%–44%)	69% (65%–72%)	92% (88%–95%)

Percentages are based on different (1) stages of HCV disease at which former IDUs were initiated on treatment, (2) uptake of antiviral therapy, and (3) response rates to antiviral therapy (i.e., compliance to treatment and clearance of the virus).

mated incidence of HCV infection in 2000 was carried forward to years 2001-2030, but clearly this rate could be influenced by the impact of future prevention initiatives; thus the numbers progressing to moderate but not severe disease could be overestimated.

Several countries have developed models to forecast the future course of their HCV epidemic, but few have validated their predictions by fitting model outcomes to past epidemiological trends relating to HCV.[41,43] The aim of this study was to capture the essential features of the HCV epidemic among IDUs—initially in Glasgow, because more epidemiological data exist for this region than elsewhere in Scotland—and calibrate model parameters with data, principally on the prevalence of IDUs, the prevalence of HCV among IDUs, and the incidence of HCV-related decompensated cirrhosis among IDUs. Insights gained from the model fitting process in Glasgow, such as on the rate of progression to cirrhosis, were used to apply the model to the whole of Scotland.

The importance of including the effect of age and sex on the progression of chronic HCV in models has been illustrated previously[41,43]; however, the potential limitation of excluding the influence of alcohol and HIV coinfection with regard to underestimating HCV disease burden has mostly only been acknowledged.[41,42] Discounting the influence of these factors on disease progression underestimated the number of IDUs developing liver failure in Glasgow during 1996-2001 by more than half that expected from the record-linkage initiative. However, the results still indicated that either (1) the prevalence of cirrhosis at 20 years was higher than the mean of 6.5% assumed; (2) the increased rate of disease progres-

sion by cofactors (age, sex, HIV coinfection, and alcohol) had been underestimated; or (3) the heterogeneity in progression had not been fully explained.

Projections clearly rely on the accuracy of the model assumptions used to derive them. Further research is needed in Scotland to examine the incidence and cessation of injecting drug use, the prevalence of heavy alcohol use by HCV diagnosis status among current/former IDUs, and mortality among current/former IDUs. It was important to model the progression to moderate disease, even with the limited data available, because patients reaching this stage are recommended for antiviral therapy.[4] The prevalence of moderate disease after 20 years of chronic HCV was based on necro-inflammation activity, which can fluctuate over time[44] but was regarded as cumulative for the purposes of modeling. Estimates of disease progression derived from community-based studies[2] would appear to be the most appropriate for population-level HCV natural history models,[45] because (1) they were generally longitudinal with known time of HCV infection, (2) recruitment was not based on presence of symptomatic or established chronic liver disease, and (3) their combined epidemiological characteristics were broadly representative of HCV-infected populations in most western countries. A comprehensive review of the literature on progression following development of compensated cirrhosis revealed higher annual rates to decompensated cirrhosis (6.5%) and HCC (3.5%) than had been used in previous model applications (4% and 0.5%-2%, respectively).[46-48]

Compared with the number of people living with chronic HCV in Scotland, relatively few have received antiviral therapy. Progress needs to be made in (1) identifying individuals who would most benefit from antiviral

therapy and (2) retention of those diagnosed with chronic HCV in clinical follow-up. A mean of 3,000 and 6,600 former IDUs were estimated to be living with moderate HCV disease in 2003 in Glasgow and Scotland, respectively; if the uptake of antiviral therapy continues at the current level, these numbers were estimated to double by 2010. As high as 16% and 27% of Glasgow former IDUs in 2005 aged 30-39 and 40-49 years, respectively, were estimated to have moderate disease, which highlights the potential benefit of targeting HCV testing at these age groups of former IDUs.

Treatment of chronic HCV with pegylated interferon plus ribavirin has been shown to be cost-effective[49] and is expected to reduce future disease complications. In France, however, it has been demonstrated that at least half of the HCV-infected population would require antiviral therapy to curb the future rise in the number of HCV-related deaths and, at most, reduce the incidence of decompensated cirrhosis by 25% over the next 20 years.[41] Increasing the uptake of antiviral therapy among former IDUs in Glasgow by up to 1,000 cases per year during 2005-2030 would have a considerable though not huge impact (38% reduction) on the future incidence of severe HCV disease. However, treatment with more effective antiviral therapies than currently available of up to 1,000 former IDUs per year with moderate HCV disease (62% of those HCV-infected by the year 2030) could potentially prevent between 38% and 84% of severe disease over the next 25 years in Glasgow. Reducing the burden of severe disease in the future involves not only increasing the numbers of infected persons in treatment but also ensuring that those treated are the ones most at risk of progressing to liver failure and cancer (*i.e.*, those with moderate disease and compensated cirrhosis rather than mild disease).

The simulations did not consider the different response to antiviral therapy according to genotype, the retreatment of nonresponders, or that patients who had not responded to antiviral therapy may have benefited from a reduced rate of liver disease progression.[50] Thus the model may have underestimated the potential long-term benefit of antiviral therapy but illustrates that current practice, with treatment of a relative minority of HCV-infected patients, will scarcely affect the future burden of this disease.

In conclusion, there is some urgency for action, because HCV is frequently asymptomatic until cirrhosis develops. Additional research regarding the cost-effectiveness of HCV testing strategies targeted at former IDUs should be pursued to help formulate public health policy in this area. The identification and treatment of a larger proportion of former IDUs with 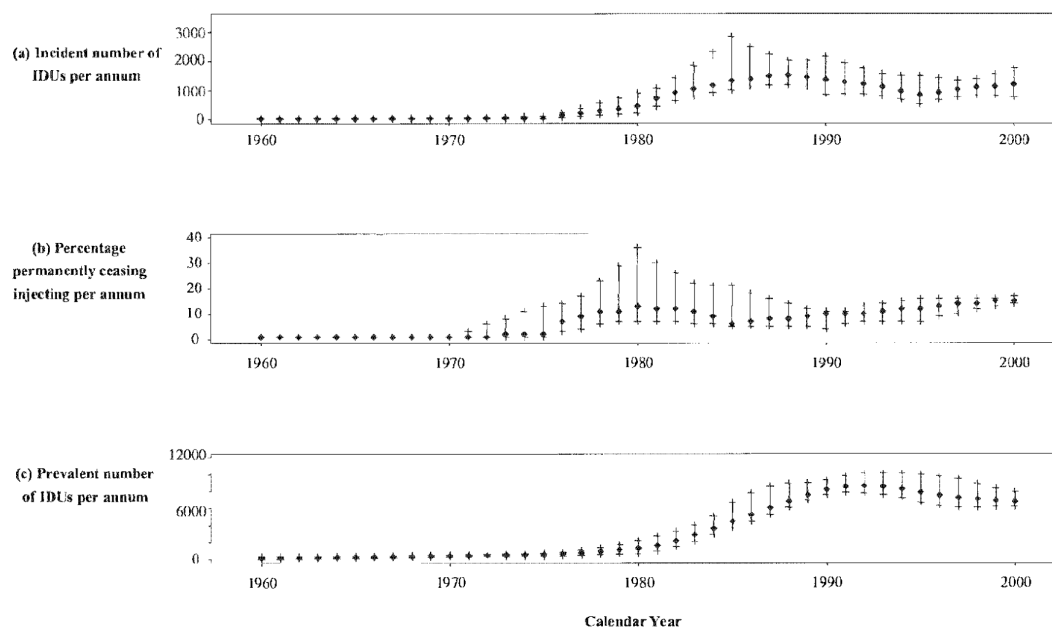advanced HCV disease, education about the importance of minimal alcohol consumption, and the development of better tolerated therapies may help to achieve a greater impact on the morbidity and mortality of this disease. Meanwhile, the development of initiatives to prevent the further spread of HCV infection among current IDUs and the initiation of non-IDUs into injecting should not be neglected.

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Appendix A

Appendix Fig. A. Estimates (10th, 50th, and 90th percentiles per annum) of incidence, cessation, and prevalence of injecting drug use in Glasgow during 1960-2000. (A) Incident number of IDUs per annum. (B) Percentage permanently ceasing injecting per annum. (C) Prevalent number of IDUs per annum.

Appendix B

The transition rates of HCV chronically infected persons following the development of compensated cirrhosis are detailed in the table and are referred to as transitions (i)-(vii). The annual probability of liver transplantation (iii) among decompensated cirrhosis cases was based on Scottish data (details available from the authors). For the remaining transition rates, pertinent English language papers were identified through the PubMed database, which was searched to the end of January 2004 using the terms *hepatitis C* and either *cirrhosis, hepatocellular carcinoma*, or *liver transplantation* and augmented by additional citations from these papers.

Quantitative data were extracted from each paper on (1) the cumulative probability $[s(t)]$ of not progressing to the outcome (or who had survived) at t years $[t = 5$ for transitions (i), (ii), (iv), (vii); $t = 2$ for (v); $t = 1$ for (vi)]; (2) the total number of subjects (n); and (3) the number (or estimate of the number) of subjects censored $[c(t)]$ before t years; probabilities $s(t)$ were converted into average annual progression rates $[i.e., 1 - s(t)^{1/t}]$ and are presented in the table. Pooled estimates (with 95% CIs) of $s(t)$ were derived using random effects,[1,2] where the variance of $s(t)$ was estimated using Peto's method[3] $[i.e., s(t)(1 - s(t)) / (n - c(t))]$, and then converted into annual progression rates as above. The 95% CI ranges of the pooled annual progression rates were used in the model.

Appendix B Table. Estimated Annual Transition Probabilities for Progression of HCV-Infected Persons With Cirrhosis

Progression Between Disease States		Average Annual Transition Rates Estimated from Literature			
Initial State	Outcome	Point Estimate	Total Number of Subjects (Mean Years of Follow-up)	Reference	Pooled Estimate (95% CI§)
(i) Compensated cirrhosis	Decompensated cirrhosis	3.9%*·†	355 (5.1)	Fattovich, et al.[4]	6.5% (4.0%–9.2%)
		4.9%*·†	112 (4.5)	Hu, et al.[5]	
		6.4%†	136 (6.6)	Fattovich, et al.[6]	
		9.1%†	44 (3.3)	Serfaty, et al.[7]	
		9.7%‡	257 (5.3)	Ginés, et al.[8]	
(ii) Compensated cirrhosis	HCC	0.7%	124 (6.1)	Takano, et al.[9]	3.5% (2.4%–4.6%)
		1.0%‡	405 (8.0)	Gentilini, et al.[10]	
		1.4%*	384 (5.1)	Fattovich, et al.[4]	
		2.1%*	112 (4.5)	Hu, et al.[5]	
		2.1%	136 (6.6)	Fattovich, et al.[6]	
		2.5%*	163 (5.3)	Bruno, et al.[11]	
		2.8%*	416 (5.7)	Degos, et al.[12]	
		3.4%‡	396 (4.2)	Mancelli, et al.[13]	
		4.6%	166 (5.5)	Chiaramonte, et al.[14]	
		4.7%	349 (5.8)	Ikeda, et al.[15]	
		5.1%‡	228 (3.7)	Imberti, et al.[16]	
		5.1%	44 (3.3)	Serfaty, et al.[7]	
		6.9%	45 (5.5)	Nishiguchi, et al.[17]	
		12.3%‡	400 (3.0)	Tsai, et al.[18]	
(iii) Decompensated cirrhosis	Liver transplantation	2.1%	507 (1.9)	Hutchinson, et al. (unpublished data)	2.0%§
(iv) Decompensated cirrhosis	Death	12.6%*	24 (DM)	Fattovich, et al.[6]	18.6% (13.7%–25.0%)
		12.9%*	65 (2.0)	Fattovich, et al.[4]	
		14.0%	49 (DM)	Hu, et al.[5]	
		22.3%	507 (1.9)	Hutchinson, et al. (unpublished data)	
		30.7%‡	121 (DM)	Ginés, et al.[8]	
(v) HCC	Death	54.0%	70 (0.7)	Hutchinson, et al (unpublished data)	60.5% (54.5%–67.6%)
		57.6%*	60 (DM)	Degos, et al.[12]	
		63.9%‡	2,573 (DM)	El-Serag, et al.[19]	
(vi) Liver transplantation (for decompensated cirrhosis)	Death in first year	5.2%	58 (3.1)	Paik, et al.[20]	14.6% (11.1%–18.2%)
		6.0%	97 (DM)	Ascher, et al.[21]	
		7.0%	54 (3.4)	Shuhart, et al.[22]	
		10.0%	128 (2.7)	Wali, et al.[23]	
		13.0%	209 (4.1)	Neumann, et al.[24]	
		16.0%	510 (2.5)	Ghobrial, et al.[25]	
		20.0%	3,084 (DM)	Detre, et al.[26]	
		21.0%	149 (3.0)	Gane, et al.[27]	
		21.8%	715 (9.4)	Jain, et al.[28]	
		22.1%	1,080 (DM)	Fagiuoli, et al.[29]	
(vii) Liver transplantation (for decompensated cirrhosis)	Death in second year or later	3.0%	149 (3.0)	Gane, et al.[27]	4.4% (3.5%–5.3%)
		3.1%	1,080 (DM)	Fagiuoli, et al.[29]	
		3.5%	715 (9.4)	Jain, et al.[28]	
		3.6%	209 (4.1)	Neumann, et al.[24]	
		5.1%	128 (2.7)	Wali, et al.[23]	
		5.1%	3,084 (DM)	Detre, et al.[26]	
		5.1%	510 (2.5)	Ghobrial, et al.[25]	
		6.5%	54 (3.4)	Shuhart, et al.[22]	
		10.0%	58 (3.1)	Paik, et al.[20]	

Abbreviations: HCC, hepatocellular carcinoma; DM, data missing.

*Includes persons who had received antiviral therapy.

†Unrelated to HCC.

‡Includes HCV antibody–negative persons.

§Range/estimate used in model.

Appendix B References

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Appendix C Table. The Modeled Prevalent Number (Mean and 95% CI) of IDUs in Glasgow and Scotland by Stage of HCV Disease and IDU Status, 2000–2030

Region	IDU Status	HCV Disease Stage	2000	2005	2010	2015	2020	2025	2030
					Calendar Year				
Glasgow	All	All IDUs	24,260 (19,060–32,650)	29,150 (22,700–37,850)	33,680 (24,890–43,230)	37,650 (26,290–49,040)	40,880 (27,170–54,140)	43,150 (27,500–59,060)	44,440 (26,940–63,020)
		All HCV infected	15,730 (12,700–20,580)	18,450 (15,050–23,330)	20,890 (16,600–26,200)	22,930 (17,270–28,870)	24,460 (17,580–31,930)	25,340 (16,990–34,270)	25,620 (16,210–35,840)
		All chronically infected	12,090 (9,710–15,800)	13,950 (11,320–17,770)	15,610 (12,150–19,960)	16,960 (12,640–22,010)	17,950 (12,590–24,110)	18,480 (12,450–25,840)	18,620 (11,890–27,020)
		Mild	9,040 (6,300–12,530)	9,270 (6,450–12,550)	9,160 (6,080–12,790)	8,910 (5,570–12,990)	8,670 (4,920–13,270)	8,490 (4,520–13,330)	8,380 (4,310–13,360)
		Moderate	2,550 (1,380–4,520)	4,040 (2,570–6,170)	5,630 (3,990–7,950)	7,050 (5,280–9,450)	8,110 (6,080–10,830)	8,700 (6,280–12,080)	8,900 (5,850–12,950)
		Severe (cirrhosis)	500 (370–660)	640 (470–880)	820 (580–1,160)	1,000 (660–1,480)	1,170 (710–1,820)	1,280 (710–2,160)	1,340 (670–2,380)
	Former	All former IDUs	17,280 (12,100–25,570)	22,540 (16,440–31,000)	27,210 (19,460–36,290)	31,260 (21,960–40,890)	34,540 (23,250–46,190)	36,820 (23,600–50,600)	38,100 (23,150–54,350)
		All HCV infected	11,380 (8,310–16,390)	14,460 (10,990–19,290)	17,050 (12,910–21,890)	19,180 (14,500–24,400)	20,760 (15,080–26,530)	21,640 (14,960–28,710)	21,910 (14,220–30,280)
		All chronically infected	8,730 (6,260–12,570)	10,900 (8,320–14,620)	12,670 (9,630–16,280)	14,100 (10,550–18,250)	15,120 (10,780–20,160)	15,660 (10,650–21,520)	15,790 (10,110–22,550)
		Mild	6,150 (3,800–9,570)	6,560 (4,280–9,700)	6,640 (4,180–9,350)	6,430 (3,800–9,360)	6,200 (3,420–9,560)	6,030 (3,150–9,540)	5,910 (2,910–9,600)
		Moderate	2,130 (1,170–3,690)	3,630 (2,300–5,490)	5,230 (3,650–7,370)	6,680 (4,900–8,980)	7,760 (5,790–10,340)	8,360 (6,010–11,360)	8,550 (5,630–12,320)
		Severe (cirrhosis)	450 (320–610)	610 (440–840)	800 (560–1140)	990 (640–1,460)	1,150 (700–1,810)	1,270 (710–2,140)	1,320 (660–2,350)
Scotland	All	All IDUs	77,480 (54,990–118,260)	89,860 (65,910–130,160)	101,830 (73,330–140,080)	112,310 (79,290–154,850)	120,700 (81,510–167,490)	126,250 (82,660–175,230)	126,680 (79,600–178,780)
		All infected	37,840 (27,960–53,160)	45,480 (34,840–63,210)	50,890 (38,230–69,000)	55,110 (40,610–74,250)	58,100 (41,010–77,340)	59,500 (40,510–80,240)	59,150 (38,710–82,680)
		All chronically infected	28,700 (21,250–40,720)	33,830 (25,620–47,340)	36,890 (27,060–50,840)	39,100 (27,260–54,080)	40,510 (26,930–57,830)	40,970 (26,180–59,680)	40,400 (23,980–60,720)
		Mild	21,500 (13,510–31,560)	22,900 (14,850–34,050)	22,020 (13,670–32,140)	20,550 (12,150–30,390)	19,270 (10,840–29,550)	18,380 (9,910–29,300)	17,660 (9,170–28,660)
		Moderate	5,640 (3,120–9,660)	9,070 (5,700–14,350)	12,640 (7,880–19,320)	15,920 (9,530–24,580)	18,270 (10,650–27,670)	19,390 (10,370–29,240)	19,480 (9,610–29,820)
		Severe (cirrhosis)	1,560 (1,300–1,920)	1,860 (1,450–2,490)	2,240 (1,650–3,090)	2,630 (1,740–3,660)	2,970 (1,760–4,610)	3,190 (1,710–5,610)	3,260 (1,600–5,940)
	Former	All former IDUs	51,460 (34,010–81,530)	69,300 (49,030–105,230)	83,290 (59,760–121,070)	94,680 (66,130–134,150)	103,520 (70,610–145,330)	109,220 (71,970–154,450)	111,430 (69,550–158,920)
		All infected	26,310 (18,190–38,640)	34,850 (25,400–50,440)	41,500 (30,840–57,980)	46,470 (34,520–63,340)	49,850 (36,110–67,060)	51,410 (36,000–69,030)	51,320 (34,550–70,930)
		All chronically infected	19,920 (13,680–29,220)	25,740 (18,600–37,490)	29,740 (21,360–42,240)	32,530 (22,510–45,940)	34,240 (22,470–49,380)	34,820 (21,530–51,690)	34,450 (20,150–51,770)
		Mild	13,860 (8,130–21,750)	16,000 (9,700–24,680)	16,040 (9,760–24,220)	15,050 (8,920–22,550)	13,940 (7,900–21,590)	13,110 (6,920–21,260)	12,560 (6,380–20,910)
		Moderate	4,640 (2,520–7,810)	7,980 (4,990–12,540)	11,530 (7,010–17,620)	14,910 (8,860–23,280)	17,370 (9,970–26,960)	18,550 (9,830–28,510)	18,660 (9,090–29,170)
		Severe (cirrhosis)	1,420 (1,140–1,780)	1,760 (1,360–2,330)	2,160 (1,600–2,950)	2,570 (1,690–3,610)	2,930 (1,740–4,560)	3,160 (1,680–5,530)	3,230 (1,580–5,800)