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Hepatitis C among drug users in Europe

Epidemiology, treatment and prevention

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Foreword

This new publication on hepatitis C among drug users in Europe is both timely and important. It is estimated that 1.6 % of the population worldwide, or 115 million people, has ever been infected with the hepatitis C virus (HCV) and that about two-thirds of the infections are active. In the European Union, an estimated 5.5 million individuals are coping with chronic infection. Drug use is central to the European HCV problem, with people who inject drugs being a key group affected by this disease — national estimates of antibody prevalence range anywhere between 15 % and 84 %. Moreover, there is still significant ongoing transmission of this disease, with new injectors often becoming infected relatively rapidly. This means that HCV prevention remains one of the major challenges for Europe's public health response to drug injecting.

In the 12 years since the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) published its last major report on this topic, *Hepatitis C and injecting drug use: impact, costs and policy options*, much has changed. Importantly, even if some challenges still exist, considerable progress has been made during this period in addressing HIV infections among people who inject drugs. Until recently, however, the situation in respect to HCV infection among this group looked far more pessimistic. There are grounds now for greater optimism, due largely to the development of new pharmacological options and a growing confidence that these can be offered in ways that are likely to be effective. For many years, the treatment of chronic HCV infection was based on therapies that required long treatment periods and had side effects that could deter compliance. For these reasons, drug users were often regarded as a difficult group to treat, treatment uptake was limited and, overall, the efficacy of interventions of all types in this area was disappointing. In the last few years, however, treatment has undergone a transformation, with new pharmacotherapies becoming increasingly available that appear to overcome many of the barriers that existed to offering effective care in this area. With these developments, treatment as prevention now emerges as a real possibility in providing an effective response to the HCV epidemic among drug injectors in Europe.

This publication provides a timely overview of how this important objective can be realised by analysing the hepatitis C epidemic in Europe, with major focuses on treatment and prevention. In these pages, you will find a state-of-the-art review of the epidemiology of HCV infection in Europe, drawing on information that includes the latest surveillance data from our partners in the European Centre for Disease Prevention and Control (ECDC) and the estimated prevalence of HCV among drug users, collated by the EMCDDA. This is complemented by information from the Reitox network of focal points, which provides an overview of the way preventive measures are currently implemented across Europe. Chapters written by international experts then address what we know about the treatment of HCV infection among people who inject drugs, with an emphasis on how we encourage uptake and deliver effective outcomes. Implementation issues are also explored, as are the complementary roles of treatment and prevention. An up-to-date overview of the new medicines currently available or in development is also provided. Importantly, how to scale up HCV treatment is explored in detail from two different viewpoints: evaluating its use as a prevention tool, and from the perspective of the drug user. This latter perspective is crucial as, in addition to effective therapies, the involvement of patients is likely to be a key element of any successful significant expansion of treatment in this area.

A clear conclusion emerging from our analysis is that, without effective action, the future costs to both individuals and health budgets of not addressing this infection among those who inject drugs, or have done so in the past, will be considerable. I am optimistic, however, because as this report clearly demonstrates, we now have an opportunity in Europe to make real and sustained progress in this area. Recent improvements in HCV therapeutic options mean that by combining treatment with adequate prevention and harm reduction measures, we now have the necessary tools to control the epidemic. We also have examples of good service models that can help us get the implementation right. It is also clear that barriers still exist to scaling up responses in this area and these urgently need to be overcome. Today in Europe, still far too many people are unaware of their HCV infection and still too many of those diagnosed with this disease lack access to effective treatment. This is a situation that needs to change. This Insights publication, I believe, makes a valuable contribution to achieving this objective, by not only identifying where the challenges exist, but also providing us with a better understanding of how improvements to the care we provide in this area can be achieved.

Alexis Goosdeel
Director, EMCDDA

Executive summary

Hepatitis C is a disease of the liver caused by the hepatitis C virus (HCV), which if not resolved can lead to chronic liver disease, cirrhosis and cancer. The disease, which affects many millions of people worldwide, is communicable and is spread by contact with infected blood or other bodily fluids. In Europe, the key risk group for HCV infection is people who inject drugs. High rates of HCV infection are commonly found in this group and people with an injecting history, however brief, as well as current injection drug users, are still unaware of their infection status. There are now new opportunities for effective treatment and prevention that, if scaled up sufficiently in Europe, could contribute to a significant reduction in the health harms associated with this disease.

This Insights publication provides both practitioners and policymakers with an analysis of the current epidemiology, harm reduction and treatment measures in relation to HCV infection in Europe. It also covers the barriers to treatment and examples of treatment scale-up and services organisation. Specifically, it provides an up-to-date overview of the new antiviral treatments that have become more available since 2014 and a review of HCV treatment initiatives in Europe. Finally, it presents and discusses modelling projections on the combined effects and synergies of different harm reduction interventions, and examines where improvements in data availability are needed to better inform policy and practice in this area.

Chapter 1 gives an insight into the size of the public health problem related to hepatitis C in Europe, both in the general population and among people who inject drugs. The chapter provides information on the estimation of the size of drug-injecting populations and describes the measures in place to prevent HCV infections among these groups. Worldwide, it is estimated that about 1.6 % of the population, or 115 million people, has ever been infected with HCV and that about two-thirds of the infections are active. In Europe, people who inject drugs, or have done so in the past, are now the main group affected. In many countries, prevalence of infection among samples of drug users is high, commonly in the range of 40–80 %. The chapter warns about new infections and likely ongoing transmission, but also about the fact that the coverage of interventions such as opioid substitution treatment and needle and syringe programmes in some countries continues to be low, when measured against international standards. The chapter identifies important gaps and limitations in our knowledge of the situation and the responses, which exist to varying degrees in many European countries. Chief among these are estimates of the number of people who inject drugs, the incidence and prevalence of HCV infection among this group, and the coverage of the main prevention interventions. Improving surveillance and monitoring in these areas is important for determining the burden of disease and assessing the impact of interventions over time.

Chapter 2 synthesises the available evidence relating to the uptake and outcomes of HCV treatment (including treatment adherence, sustained virological response, reinfection and morbidity related to liver disease) among people who inject drugs. The analysis suggests that treatment of HCV infection can result in acceptable outcomes in individuals who report current injecting drug use and who meet standard eligibility criteria for commencing HCV treatment. Further work is needed to assess the risk of HCV reinfection among those who are actively injecting illicit drugs. It is likely, however, that this risk can only be accurately assessed once treatment is scaled up and more equitably provided in this population.

Chapter 3 discusses the strategies to improve hepatitis C care and to enhance treatment uptake and adherence among people who inject drugs. It highlights the importance of case-finding and access to testing and also of co-location of hepatitis C treatment with community/specialist drug treatment. Three national examples of models of care from Europe are presented, with the coordinated actions and outcomes of these initiatives, including in prison settings. The chapter concludes that new hepatitis C treatment regimens, which are easy to administer and well tolerated, will make it easier in the future to deliver comprehensive, multidisciplinary care to people who inject drugs. The chapter also reviews examples of good practice from different countries, which show that there is no single solution and that even when countries have good national policy plans, room can exist for improvements in their implementation.

Through modelling, Chapter 4 analyses the strong theoretical basis for combining hepatitis C treatment with other primary prevention measures in order to reduce HCV transmission to negligible levels (so-called elimination). In most of Europe, the data suggest that after treating people with cirrhosis the next priority would be treating active injectors, even if they only have mild to moderate levels of the disease — as a greater benefit can be achieved by preventing onward transmission from this group than by delaying treatment until they develop cirrhosis and become eligible, or cease injecting. Furthermore, hepatitis C case-finding and treatment in prison could be a critical component of scaling up hepatitis C treatment in the community. The model projections described in this chapter provide strong evidence for the hypothesis that hepatitis C treatment of people who inject drugs will be essential to reduce prevalence of HCV infection and that treating this group is cost-effective. Empirical data and evaluations of the impact of scaling up hepatitis C treatment among people who inject drugs in European settings are, however, urgently needed to confirm the conclusions of the currently available statistical models.

Chapter 5 points out that treatment of HCV infection has changed dramatically and that all-oral, shorter, and better tolerated interferon-free regimens now prevail. The number of treatment options is increasing, and the chapter reviews the medications currently available and those that are in development. It provides an update on the current HCV treatment regimens (2016) and an insight into the future regimens that are likely to become available.

Chapter 6 discusses how the scaling up of HCV treatment can take into account the needs and perspectives of people who inject drugs. It draws on qualitative research among people who inject drugs to illustrate enabling interventions and their role in facilitating HCV treatment engagement, initiation and access.

Chapter 7 explains that there is currently a window of opportunity to generate empirical data and conduct evaluations of the impact of scaling up HCV treatment among people who inject drugs in European settings, as treatment services are geared up to identify and deal with severe liver disease. The analysis builds on the HIV experience and discusses the implications for HCV, to draw a framework for evaluating the scale-up of HCV treatment as prevention for people who inject drugs.

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Introduction

Matt Hickman, Natasha Martin, David Goldberg, Gabriele Fischer, Erika Duffell and Roland Simon

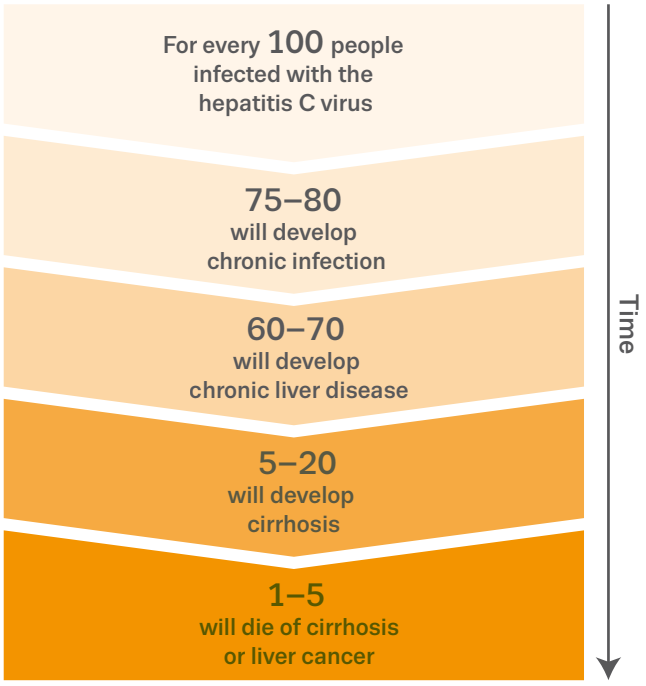
Hepatitis C virus (HCV) is an important cause of liver cancer in Europe. The key risk group for HCV infection is people who inject drugs. Preventive interventions targeting people who inject drugs will reduce transmission of the virus and future liver disease-related morbidity in Europe. Many people with an injecting history, however brief, as well as current injecting drug users, are unaware of their infection status. In part this is because initial infection with the virus is often asymptomatic, with spontaneous clearance of HCV occurring in 18–34 % of infected individuals. The remainder become chronically infected, meaning that they remain infectious to others and are at subsequent risk of developing liver disease, including cirrhosis and hepatocellular carcinoma.

Among those with chronic HCV infection, the risk of progression to cirrhosis of the liver is estimated to be 5–20 % over 20–30 years (Figure 1). Once cirrhosis has developed, the annual risk of hepatocellular carcinoma is 1–5 % and the annual risk of hepatic decompensation is 3–6 %. Following an episode of decompensation, the risk of death in the following year is between 15 % and 20 %.

The total number of people living with chronic HCV infection in Europe and the proportion infected through injecting drug use are uncertain. However, surveillance and laboratory testing of people who inject drugs shows that in many sites, at least 50 % of this group may have been infected with HCV. Opioid substitution treatment and the provision of sterile injecting equipment through needle and syringe programmes are the traditional forms of primary prevention — and where provision is optimal, considerable numbers of infections will have been prevented. But, if progress towards the elimination of hepatitis C is to be made, additional interventions for this population are required.

FIGURE 1

Risk of progression to different disease states among those infected with HCV



Source: http://www.cdc.gov/hepatitis/HCV/PDFs/HepCGeneralFactSheet.pdf

We live in exciting times for HCV prevention — which is why we have produced this new 'Insight' into HCV. Hepatitis C and HCV-related liver disease in Europe can be prevented. The critical change has been the arrival of new drug therapies, as outlined in Chapter 5. New all-oral combinations of direct-acting antiviral drugs can eliminate infection in more than 90 % of cases, are safe and treatment duration is short (only 8–12 weeks). Furthermore, in contrast to existing treatments, the new drugs are effective in those with severe liver disease and against all genotypes of HCV. However, these treatments come at a cost — up to EUR 70 000 per course — and Pawlotsky (Chapter 5) points out that the high costs could become a barrier to widespread scale-up of HCV treatment. Guidelines issued by the European Association for the Study of the Liver (EASL) in 2015 recommend, for the first time, that treatment be provided to people — such as active injectors — at risk of transmitting infection to others, irrespective of disease stage.

The prevalence of HCV-related end-stage liver disease and mortality is increasing. Chapter 1 describes the epidemiology of HCV in Europe. It is estimated that over 5 million people in Europe have chronic HCV infection. In many European countries more than half of those who inject drugs have been infected with HCV, and such individuals constitute the largest risk group for HCV infection in Europe. However, the prevalence of severe liver disease among infected drug injectors remains unknown. Nor is it clear how many people who inject drugs have been treated for HCV infection. In addition, knowledge of the coverage of other key HCV primary interventions — opioid substitution treatment and needle and syringe programmes — is also patchy. Moreover, in many countries there are no reliable estimates of the population currently at risk of HCV infection through injecting drug use. Developing better surveillance and evidence on HCV in Europe is important and will require collaboration between the EMCDDA and the European Centre for Disease Prevention and Control (ECDC) and among individual countries.

The immediate priority across Europe is to scale up HCV treatment in people with severe liver disease to reduce HCV-related morbidity and mortality, as rapidly as possible. Thereafter, the question is which patients should be prioritised for treatment next — should countries target those with moderate liver disease (pre-cirrhotic) or infected active injectors, most of whom will have no or mild disease, as recommended by EASL? In other words, should a twin strategy that uses HCV treatment to prevent HCV-related liver disease deaths while also aiming to minimise HCV transmission and start to reduce HCV prevalence in the population be adopted? Chapter 4 emphasises the importance of HCV treatment — it is unlikely that the combination of opioid substitution treatment and needle and syringe programmes in itself will achieve substantial reductions in HCV prevalence among people who inject drugs. So far, the evidence, based on model projections, is theoretical. It suggests that prioritising early HCV treatment on people who inject drugs is likely to be highly cost-effective — but as yet we lack direct evidence (i.e. that HCV transmission is reduced as a result of scaling up HCV treatment).

The reason for a lack of direct evidence is in part because HCV treatment rates among people who inject drugs historically have been low, despite evidence, as described in Chapter 2, that outcomes among this group can be as good as in other patient groups, but also because studies, designed to evaluate the impact of the prevention impact of treatment, have not been done. In the context of what was the interferon era and the complexities of treating active injectors with a drug regimen which was lengthy, was not always effective, involved weekly injections, usually in a hospital setting, and was associated with serious adverse effects, this was understandable. With the new treatments, however, these barriers do not exist. Chapter 3 argues that national strategies, and perhaps a European strategy, are required to redesign and co-locate treatment services for managing HCV infection with specialist drug services for injecting drug users.

However, this is only the first step in addressing stigma and promoting patient-facing treatment services for drug injectors, as highlighted in Chapter 6.

Certainly, there is now a window of opportunity to generate empirical data and conduct evaluations of the impact of scaling up HCV treatment among people who inject drugs in European settings, as treatment services are geared up to identify and deal with severe liver disease. How and where the evaluation should be conducted is complex, as discussed in Chapter 7. Ideally, potential intervention sites will have established 'HCV treatment-in-the-community' services, integrated with others that manage and support people who inject drugs, and critically sites will need to have mature systems for collecting data on behaviour, HCV transmission and HCV prevalence among this client group, and on HCV testing and treatment.

In the context of the EASL guidelines and the changing therapeutic landscape of HCV, such an evaluation needs to be done now and as quickly as possible.

CHAPTER 1

Hepatitis C virus infection among people who inject drugs: epidemiology and coverage of prevention measures in Europe

Isabelle Giraudon, Dagmar Hedrich, Erika Duffell, Eleni Kalamara and Lucas Wiessing

Introduction

Hepatitis C is a disease of the liver caused by a virus, which if not resolved can lead to chronic liver disease, cirrhosis and cancer. The disease is communicable and is spread by contact with infected blood or other bodily fluids. Worldwide, it is estimated that about 1.6 % of the population, or 115 million people, has ever been infected with the hepatitis C virus (HCV) and that about two-thirds of the infections are active (Gower et al., 2014). Recent estimates for the World Health Organization (WHO) European region, which in addition to the countries of the European Union and its candidate countries, includes the countries of the former Soviet Union among others, put the size of the HCV-infected population at between 9 million (Gower et al., 2014) and 15 million (Hope et al., 2014). In developed countries, injecting drug use is the most common route of transmission of the virus, as the infection can be easily transmitted from an infected injector to another when the needles and syringes or other injection equipment are shared; elsewhere nosocomial transmission (that is, acquired in hospitals and other healthcare facilities) and other routes of transmission are the most common. Thus, in Europe, people who inject drugs, or have done so in the past, are now the main group affected (Alter, 2011; Hajarizadeh et al., 2013; Stephenson, 2001; Wiessing et al., 2008).

Hepatitis C is an important public health problem as chronically infected individuals are at risk of serious long-term health consequences, including liver fibrosis, cirrhosis and hepatocellular carcinoma (Shepard et al., 2005). In Europe, hepatitis C is a leading cause of cirrhosis and primary liver cancer (Blachier et al., 2013) and evidence suggests that this burden is high (Blachier et al., 2013; Lavanchy, 2004, 2011; Sweeting et al., 2007). Worldwide, approximately 500 000 people die each year from hepatitis C-related liver diseases (WHO, 2015).

In this context, this chapter aims to give an insight into the size of the public health problem related to hepatitis C in Europe, both in the general population and among people who inject drugs. In addition to data on the epidemiology of hepatitis C, the chapter also provides information on the estimation of the size of drug-injecting populations and describes the measures in place to prevent HCV infections among these groups.

Sources of data

The epidemiology of hepatitis C reported here is based on two principal types of data: notifications of newly diagnosed cases and studies on the prevalence of antibodies to the virus among the general population and, more often, among populations of injecting drug users. Between 1995 and 2008, data on hepatitis C notifications were collected by the EMCDDA each year through its network of national focal points as part of an annual reporting exercise on the drug phenomenon in Europe ([1]). The national focal points used a standard questionnaire to report aggregated data provided by health authorities in the EU Member States, Turkey and Norway. The countries were asked to report the total number of cases of HCV infection notified by physicians, where possible identified as acute or chronic cases, as well as the case definitions

([1]) Information on the monitoring of infectious diseases among drug users is available on the Drug related-infectious diseases key indicator page on the EMCDDA website.

used. The questionnaire also asked for the number of cases with known risk factor and the number attributed to injecting drug use. From this information, it is possible to observe trends in the total number of notified cases of hepatitis C, and in the proportion of people who inject drugs among the cases with valid information on exposure category (Wiessing et al., 2008).

Since 2009, the EMCDDA works closely with the European Centre for Disease Prevention and Control (ECDC), the EU agency to which national hepatitis C notification data are now reported. ECDC facilitates the surveillance of communicable diseases through the European Surveillance System (TESSy), a web-based database for the submission and retrieval of data from 31 EU/EEA countries (the 28 EU Member States, Norway, Iceland and Liechtenstein). Data are collected from national notification systems using standardised case definitions (Duffell et al., 2015; ECDC, 2015).

National notification data for hepatitis C, however, are often unreliable due to under-diagnosis (many new infections are asymptomatic) and under-reporting of diagnoses. An additional limitation to this category of data is the incorrect classification, or lack, of information on risk group, such as injecting risk. For this reason, the EMCDDA monitors HCV antibody prevalence among drug users, as a complement to the notifications data. Data from HCV antibody prevalence studies among people who inject drugs provide complementary information and are often more informative, as the studies have usually been designed to look at populations of drug injectors, in different settings such as drug treatment, low-threshold facilities or prisons. Such studies tend to be more informative because they can differentiate between subgroups of drug injectors, by age or injecting duration, which allows to better identify recent infections and those that have so far been undiagnosed. Prevalence studies, also called 'bio-behavioural' studies, often include the collection of behavioural data, such as whether the persons underwent HCV testing or whether they are or have been sharing injection equipment and what knowledge they have about ways to prevent infection. Many European countries are able to conduct regular prevalence studies among people who inject drugs. The methods used, however, may vary: studies may have different designs, such as ad hoc versus routine testing; the data may lack national coverage and some studies also may have poor continuity over time.

Analysis of HCV antibody prevalence among subgroups of people who inject drugs — those who are younger than 25 years or have been injecting for less than 2 years — is also carried out by the EMCDDA as part of the general monitoring activity of the DRID epidemiological key indicator, in order to obtain a proxy estimate of incidence of infection (the rate of new cases occurring).

Notifications (through ECDC) and prevalence data analysed in this chapter were submitted to the EMCDDA in the 2015 national reporting round (the data are available in EMCDDA, 2016b, under infectious diseases). Whereas the notifications refer to the year 2014, data from prevalence studies refer to 2014 or the most recent year available.

In addition to data collected and analysed by the EMCDDA, this chapter incorporates the findings of a number of key publications in its description of the epidemiology of hepatitis C.

Estimates of the numbers of people injecting drugs are important in projecting the future epidemiology of HCV infection and in planning and evaluating the public health responses to the problem. As part of its routine monitoring, the EMCDDA gathers data on the numbers of people injecting drugs and on the principal relevant harm reduction responses in this area — opioid substitution treatment and needle and syringe provision through specialised programmes — from the Reitox network of national focal points. These data are also presented in this chapter.

Hepatitis C testing and reporting

Anti-HCV tests are used to detect the presence of antibodies to HCV in blood samples. A positive test result indicates that a HCV infection has occurred. Routine screening for antibodies to HCV is usually carried out with an enzyme-linked immunosorbent assay (also known as an enzyme immunoassay or ELISA). These tests cannot distinguish between an active (acute or chronic) and a resolved infection.

Tests on HCV viral material (RNA) can identify an active infection. HCV RNA can be found in the blood within 1 to 2 weeks after exposure to the virus (Fox, 2013). This test may be done to double-check a positive result on an anti-HCV antibody test, measure the level of virus in the blood (called viral load), or show how well a person with HCV is responding to treatment.

Chronic infection is defined as detectable HCV-RNA for at least 6 months. A resolved infection will have no further health consequences, whereas a chronic infection may lead to serious liver damage and premature death over the course of decades.

Definition: People who inject drugs

The EMCDDA definition for the monitoring of the prevalence of drug-related infectious diseases refers to 'ever injectors among people tested in (mostly) drug service settings'. Thus, where the study settings are specific for active injectors (e.g. needle and syringe programmes), it is likely that the sample consists only of active injectors. In other drug service or treatment settings, it might also include ever injectors who do no inject any longer. The providers of each dataset reported to the EMCDDA are asked to specify whether it refers to active injectors or to ever injectors (including active injectors) and in the latter case to provide an estimate of the proportion of active injectors.

Epidemiology

Notifications of hepatitis C in Europe

In 2014, 35 321 cases of hepatitis C were reported to ECDC in 28 countries (Iceland, Norway and all EU Member States except for France and Spain) (ECDC, in press). The overall notification rate was 8.8 cases per 100 000 population. Of these cases, 1.3 % were reported as acute, 13.3 % as chronic, 74.7 % as 'unknown' and 10.7 % could not be classified. In 2014, of the cases for whom gender was reported, 21 926 were males (11.6 per 100 000) and 12 063 were females (6.1 per 100 000), with a male-to-female ratio of 1.8 to 1. Just over half (51 %) of all hepatitis C cases reported in 2014 were aged between 25 and 44, and 8 % of cases were aged under 25 years.

National data on hepatitis C notification rates reported in 2014 are insufficient to describe the geographic distribution of newly diagnosed cases in Europe. Looking at countries that have surveillance systems which are known to capture data on both acute and chronic cases, a picture emerges of countries reporting relatively high rates of new diagnoses (Austria, Estonia, Finland, Ireland, Latvia, Norway, Sweden, United Kingdom) all located in the north of Europe, and those reporting low rates (Bulgaria, Croatia, Cyprus, Denmark, Greece, Malta, Romania, Slovenia) primarily located in the southeast. In addition to being incomplete, the data available on hepatitis C notifications are strongly influenced by national screening strategies and the measures in place in each country to prevent the transmission of the virus. These factors compound the limitations of surveillance data for a disease such as hepatitis C, which is largely asymptomatic until a late stage. Notifications may hugely underestimate the real number of new infections and they may reflect testing practices rather than real occurrence of disease (Duffell et al., 2015; Hagan et al., 2002). There are also possible large differences in reporting completeness between countries.

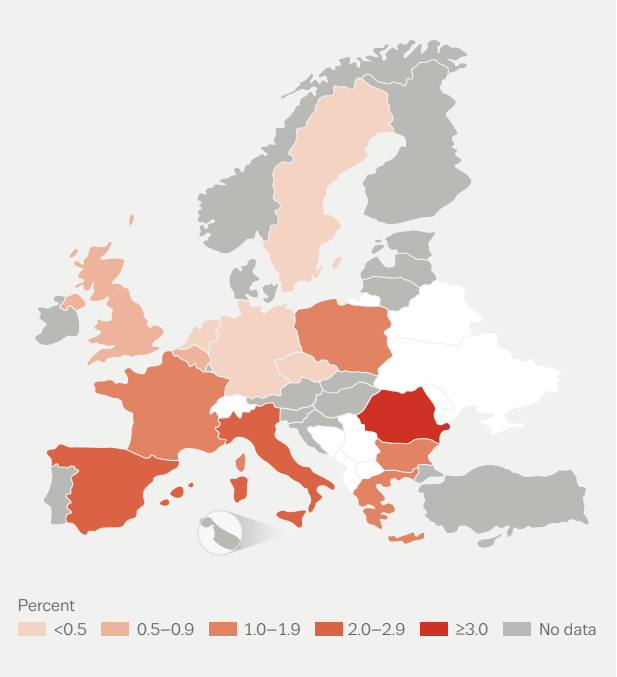
Data regarding the most likely mode of transmission of hepatitis C virus were provided for only 16 % (range 0–79 %) of the cases reported in 2014. The overall completeness of data on transmission has declined since 2011, when it was 29 %. Overall, the most commonly reported route of transmission among newly diagnosed cases of hepatitis C was injecting drug use, accounting for 78 % of all cases with a known transmission route. Although the data are incomplete and it is difficult to draw any firm conclusions, there are differences in reported transmission routes between countries. While nosocomial transmission appears to be an uncommon route of transmission in most European countries, it has been a commonly reported route in Italy, Latvia, Romania and Slovakia, although differences in reporting still hamper a clear interpretation of the data. Among countries with more complete reporting there are still major differences, with injecting drug use accounting for over 80 % of all reported cases with a known route of transmission in Finland and Ireland but fewer than 10 % of cases in Romania, suggesting that real differences may exist in HCV transmission patterns between countries (Duffell et al., 2015; Wiessing et al., 2008).

HCV antibody prevalence

The prevalence of antibodies to HCV among the general population in Europe is not systematically monitored by national health systems. What information is available comes from a variety of studies carried out over periods of different durations and with various sampling strategies.

A recently published review searched the international scientific literature for reports of antibodies to HCV among the general population published between 1 January 2000 and 27 July 2009 (Hahné et al., 2013). In the review, 13 EU Member States and Turkey were found to have at least one estimate, although only four of the estimates were at national level and some estimates were nearly 20 years old. Among these countries, the prevalence of anti-HCV in the general population varied from 0.1 % to 3.5 %, with the highest levels found in

FIGURE 1.1
Estimated prevalence of antibodies to HCV in the general population in Europe



Adapted from Hahné et al., 2013.

countries in the south and east of Europe and the lowest in the north (Figure 1.1 and Annex Table A1). In addition to the data reviewed by Hahné et al. (2013), new or more recent estimates based on national health surveys are available for a number of countries including France (Meffre et al., 2010), Germany (Poethko-Müller et al., 2013), Lithuania (Liakina and Valantinas, 2012), the Netherlands (Vriend et al., 2012) and Slovakia (Schréter et al., 2007). Among these countries anti-HIV prevalence in the general population ranged from 0.3 % to 2.8 %. Trends, where the most recent data are compared with the previous estimates available, show an increase in the Netherlands (0.3 %) and a decrease in France (0.8 %) and Germany (0.3 %). In Lithuania (2.8 %) and Slovakia (1.5 %), the available estimates sit within the values seen in other European countries, and no trend analysis can be made by comparison to previous data.

Hope et al. (2014) collated data on anti-HCV prevalence in studies on the general population, and these varied from 0.4 % to 5.2 %. They also assembled a data set on the prevalence imputed from antibodies to HCV in blood donors for almost all EU countries. This data set contains a greater range of national values: from 0.1 % to 10.3 %. Here too, nevertheless, the highest prevalence levels tend to be found in countries in the east and in the south, with imputed HCV prevalence levels of 10.3 % in Lithuania, 9.2 % in Romania, 7.0 % in Estonia and 4.5 % in Bulgaria. However, considering that notable differences were found between the two variables for a number of countries, and that blood donors are a very specific group within the population, of which they are unlikely to be representative, caution is needed when interpreting these results.

From the estimates made by Hope et al. (2014), 7.4 million people living in the European Union have antibodies to HCV, indicating a current or resolved infection. Of these, an estimated 5.5 million have a chronic infection.

HCV among the drug-injecting population

Across Europe, among people who inject drugs — which for this analysis includes those who have ever done so — a history of infection with HCV is very frequent and HCV antibody prevalence is overall high. Hahné et al. (2013) found that the estimate of anti-HCV prevalence in people who inject drugs, based on the data collected by the EMCDDA, was on average almost 50 times higher than that in the general population, in the 13 countries that had both estimates available. In more recent data obtained by the EMCDDA, 13 countries reported on anti-HCV prevalence among national samples of drug injectors for the years 2013 or 2014. Anti-HCV prevalence ranged from 15 % to 84 %, with six of the countries reporting rates in excess of 50 % (Figure 1.2).

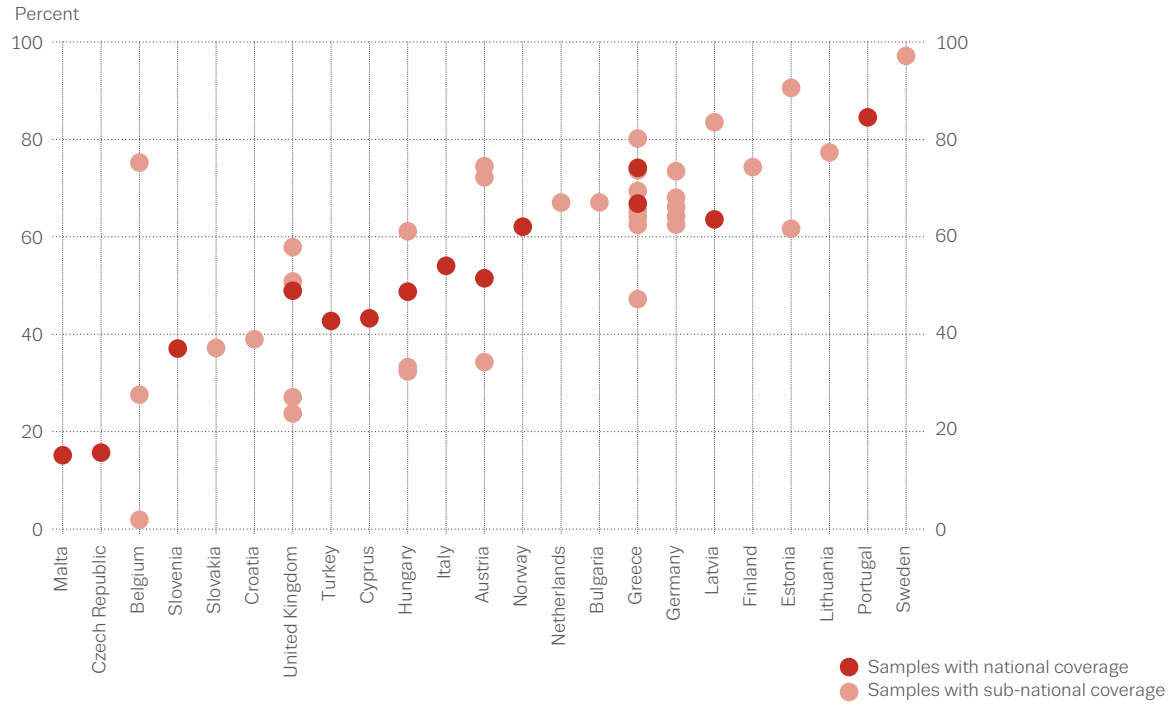
Monitoring of anti-HCV prevalence within populations over time provides an indication of possible changes in the transmission of the virus. Among countries with national trend data for the period 2008–14, six (Greece, Latvia, Hungary, Slovenia, United Kingdom, Turkey) observed an increasing trend in HCV-antibody prevalence among injecting drug users, while Malta and Norway observed a decrease. Beyond national trends, trend data in sub-national sources are important as well, as shown by increases reported in several areas in Europe recently (EMCDDA, 2015). Trends at sub-national level show, for example, local increases in Budapest (Hungary), Sofia (Bulgaria) and Vienna (Austria) (EMCDDA, 2016a).

An increase in HCV prevalence among people who inject drugs has previously been associated with an increased risk for injection-related HIV outbreaks, and therefore increases should be monitored carefully (EMCDDA, 2015; Vickerman et al., 2013).

As approximations of recently acquired infections or incidence, the EMCDDA monitors the prevalence of anti-HCV among young injectors (under age 25) and among new injectors (those who have injected for less

FIGURE 1.2

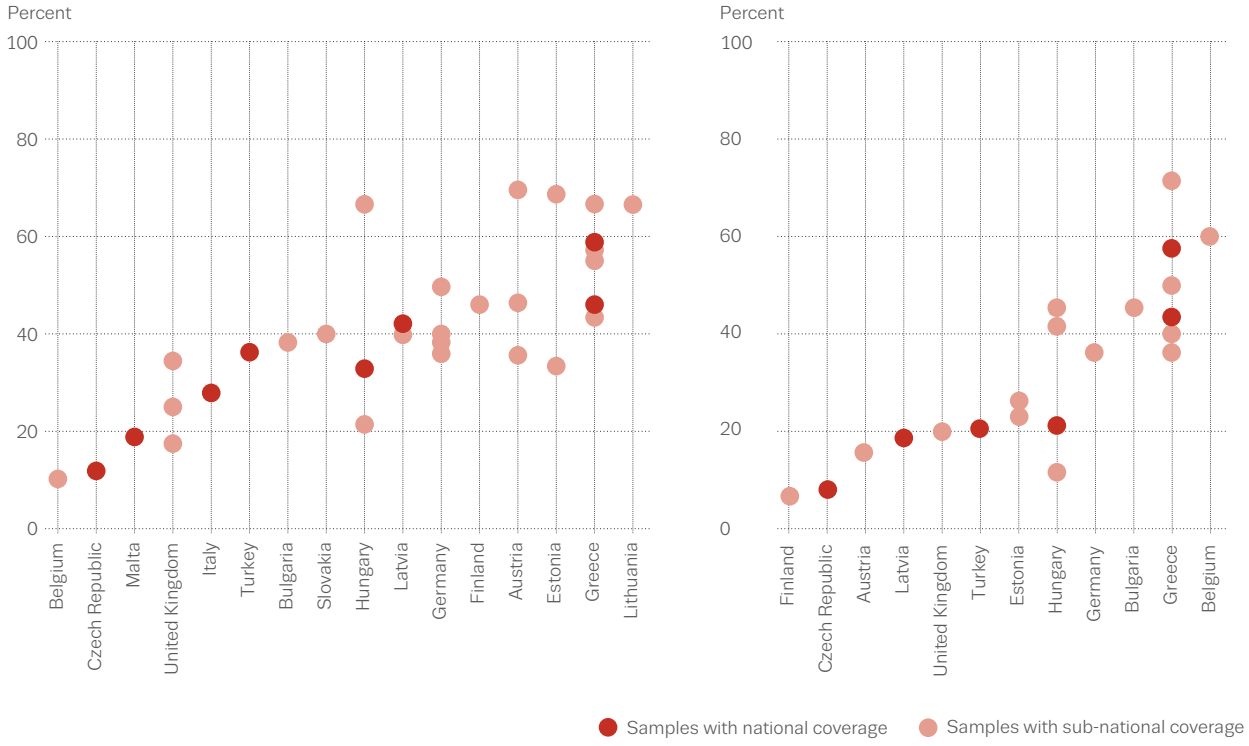
Anti-HCV prevalence (%) among people who inject drugs in the European Union, Norway and Turkey, 2013–14



Source: Studies with national and subnational coverage covering the period 2013–14, reported to the EMCDDA by Reitox national focal points.

FIGURE 1.3

Anti-HCV prevalence (%) among people who inject drugs under age 25 (left) and among those injecting for less than 2 years (right) in the European Union, Norway and Turkey, 2013–14



Source: Studies with national and subnational coverage covering the period 2013–14, reported to the EMCDDA by Reitox national focal points.
NB: Samples of less than 10 persons are not included.

than 2 years). Estimates for these groups of drug injectors are available only for a sub-set of countries, and are often based on small samples. Overall, they indicate anti-HCV prevalence levels of over 20 % and typically between 20 % and 60 % in these groups. Many of the countries reported samples where anti-HCV prevalence is 40 % or more among young injectors, suggesting high levels of transmission in recent years (Figure 1.3).

Estimates of anti-HCV prevalence among new injectors ranged from 7 % to 71 % in the 11 countries providing recent data. In common with the findings on anti-HCV prevalence among injecting drug users of all ages and injection history, the highest estimates among new injectors were in the south or east of Europe (Figure 1.3).

Of these two indicators for recent infection, the prevalence among new injectors is the strongest proxy for incidence of HCV infection, given that even young injectors, under age 25, may have already injected for a number of years. However, data on young injectors may help validate the data on new injectors and provide insights where prevalence among new injectors is not available. The data available are likely to be subject to limitations, particularly those that affect small samples such as the subgroups of young or recent injectors.

There are also general limitations to the prevalence data. Thus, studies among drug injectors are often limited to 'convenience samples' of those attending drug services, where no systematic sampling has taken place or where procedures and testing completeness are not reported. Studies are also often local or regional with unknown generalisability to the national level. Due to these limitations, it is difficult to generalise findings from these samples to people who inject drugs as a group. Nevertheless, following changes in prevalence over time — in the same settings in particular — may provide valuable information.

Incidence

Studies reporting on the incidence of primary HCV infection among people who inject drugs in Europe have been reviewed by Wiessing et al. (2014). In total, 27 studies were found that reported direct measurements of HCV incidence, covering only nine EU Member States (Czech Republic, Denmark, Finland, France, Ireland, Netherlands, Spain, Sweden, United Kingdom). In these studies, the incidence of HCV among people who inject drugs was often high (range 2.7–66 per 100 person-years, median 13). The review found that data on incidence of HCV infection among people who inject drugs were sparse across Europe, of variable quality and not easily comparable. Some of the studies had limitations such as being old, conducted in specific settings or local. For example, a study in France in 2000; a prison study in the Netherlands in 1997; an Irish estimate based on one study in Dublin in 1992–1999; a needle and syringes programme in Malmö, Sweden. While the review covered literature published from 2000 to 2012, studies more recent than 2005 were found only for the Netherlands and the United Kingdom.

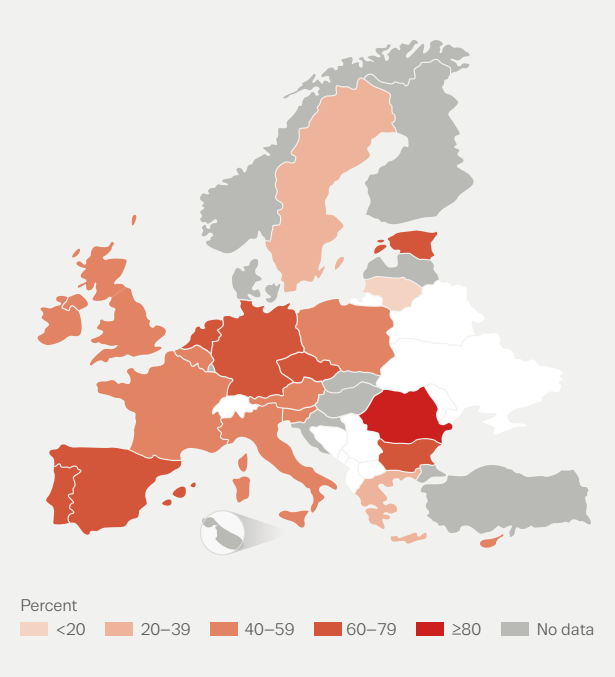
Genotype

Hepatitis C virus can be classified into seven strains or genotypes, numbered 1 to 7, and 67 subtypes (Smith et al., 2014). Some of the genotypes (1a, 1b and 3a) have become distributed widely because of transmission through blood transfusion and needle-sharing among people who inject drugs and now represent the vast majority of infections in developed countries. These are the genotypes that are most commonly encountered in clinical settings and for which most information has been collected on response to antiviral treatments (Simmonds, 2004). Information on genotype is important because the response to traditional antiviral treatment (which before 2011 was based on combination therapy with interferon and ribavirin) varies by genotype and therefore treatment has to be tailored accordingly (Muir, 2014; WHO, 2014; see also Chapter 4).

In a review of HCV epidemiology (Wiessing et al., 2014), 36 studies with genotype data were identified from 20 EU countries, including samples for nearly 6 000 HCV-infected people who inject drugs which were identified to the level of genotype or subtype. HCV genotypes 1 and 3 (subtypes 1a and 3a) are the most commonly identified among drug injectors in Europe. The data suggest that genotype 4, prevalent in the Middle East and Africa, particularly in Egypt (Kamal and Nassar, 2008), may be increasing. Distribution of the genotypes varied among drug injectors across Europe (Figure 1.4), with the traditionally difficult-to-treat genotypes (1 and 4) being predominant in certain EU countries (in particular Portugal, Romania and Spain), and showing a large variation (17–91 %) and a median of 53 %. Caution must be exercised in analysing these findings for a number of reasons: not all reports assessed mixed infections; estimates for six of the countries are based on samples of fewer than 100 patients; for 10 countries only one study could be located and some studies were based on selected populations (such as hospitalised patients).

FIGURE 1.4

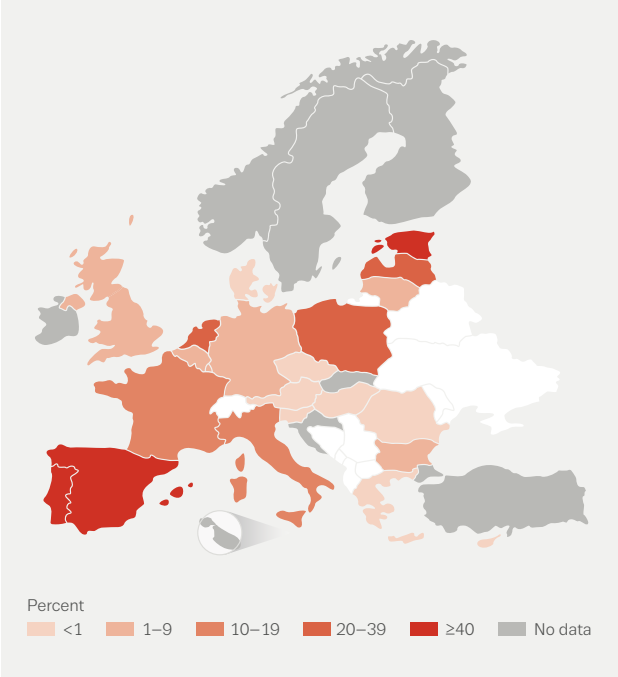
Proportion (%) of HCV infections among people who inject drugs that are genotypes 1 or 4



Adapted from Wiessing et al. (2014).

FIGURE 1.5

Co-infection with HIV among HCV-infected people who inject drugs



Adapted from Wiessing et al. (2014).

HIV co-infection

Co-infection with HIV is another factor that influences treatment outcome. Thirty-three published and 15 unpublished studies were reviewed by Wiessing et al. (2014), resulting in 68 HIV–HCV co-infection estimates for people who inject drugs in Europe. It should be noted that as HCV infection was not confirmed by RNA in many studies, antibody prevalence was used across all studies. Estimates of HIV–HCV co-infection prevalence were available for 22 countries in Europe and 11 countries had multiple estimates. Among HCV-infected people who inject drugs, co-infection with HIV ranged from 0 to 70 %, with a median of 3.9 %. The rate of HIV co-infection correlated with the HIV prevalence among the group. HIV prevalence among people who inject drugs differs greatly across Europe (from 0 to 30 %). Among those infected with HCV, the range is even wider as this is a high-risk group. Levels of co-infection prevalence can be classed as low (not more than 4 %) in 11 countries, moderate (5–15 %) in three countries and high (over 15 %) in seven countries (Figure 1.5).

Burden of disease, cirrhosis, hepatocellular carcinoma and mortality

Information on the current and projected impact of HCV infection in terms of disease burden and mortality is necessary to inform public health planning and resource allocation. Burden of disease studies aim to quantify the effect of an illness in terms that are comparable across populations and between diseases. Data on the burden of disease of hepatitis C in Europe are scarce, outdated or inconclusive (Mühlberger et al., 2009).

The review conducted by Wiessing et al. (2014) found seven papers that reported on the burden of disease or mortality related to HCV infection among people who inject drugs in the European Union. Where assessed, the disease burden of HCV was found to be high and is expected to rise in the next decade. Only two of the 27 countries included in the review appeared to have carried out a modelling study to estimate the effect of HCV treatment on the future burden of disease. Without treatment, a study in the Netherlands (Amsterdam) projected a 36 % increase in the occurrence of decompensated cirrhosis or hepatocellular cancer, between 2011 and 2025 (Matser et al., 2012), whereas in Scotland, UK (Glasgow) increases of 56 % in cirrhosis and 64 % in mild liver disease were projected for 2010–2025. Both studies showed that HCV treatment

would substantially reduce the burden of liver disease (Hutchinson et al., 2005).

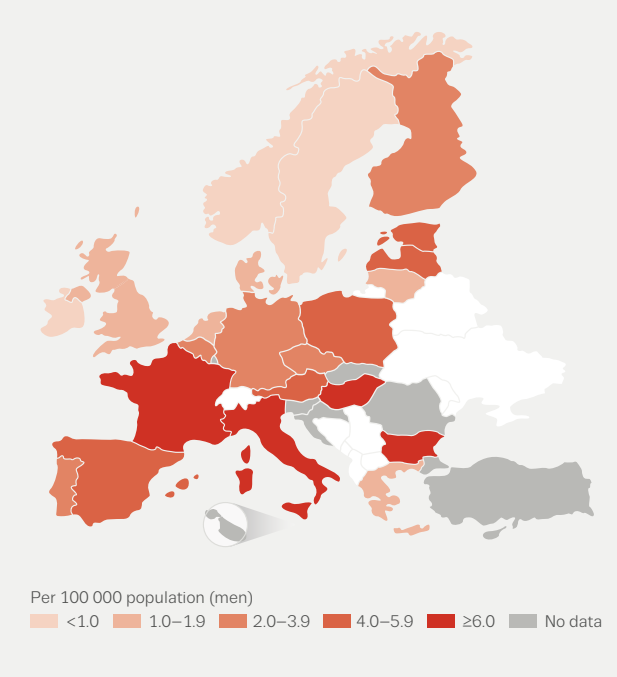
Mortality in HCV-infected people who inject drugs is dependent on competing mortality (e.g. HIV or drug-related death) and the duration of persistent HCV infection. In the review, all-cause mortality rates among HCV-infected drug injectors were estimated at 2.1–2.4 per 100 person-years in Spain (Hernando et al., 2012) and the Netherlands (Grady et al., 2011). A much higher rate was estimated for injectors co-infected with HIV in Denmark, where all-cause mortality was estimated at 12.2 per 100 person-years (Omland et al., 2010). The high mortality rate in the Danish study may be explained by high rates of overdose mortality or differences in combination antiretroviral therapy initiation, given that a Spanish study reported a crude mortality rate of 2.4 per 100 person-years among HIV co-infected people who inject drugs during a comparable study period. This suggests the existence of significant differences between countries in mortality rates among HIV-infected people who inject drugs, as is found for mortality among all drug injectors, and underlines the importance of obtaining country-specific mortality estimates. Available data on the morbidity and mortality risk due to HCV among people who inject drugs are scarce but are urgently needed for future planning. More recent large cohort studies also show that liver disease (including viral hepatitis and cirrhosis) is one of the major causes of deaths among drug users (Pierce et al., 2015).

The HCV disease burden among people who inject drugs translates to a significant burden in the general population. Approximately 500 000 people worldwide die annually (2.7 % of all deaths) from hepatitis C-related liver diseases, most commonly liver disease including liver cancer (WHO, 2015). An estimated 57 % of liver cirrhosis cases and 78 % of primary liver cancers result from HBV or HCV infection (WHO, 2013). Globally, 27 % of all cases of cirrhosis and 35 % of all cases of hepatocellular cancer are attributed to HCV infection (Bosetti et al., 2007, 2008; WHO, 2013).

In Europe, annual mortality rates from hepatocellular cancer vary by country and are generally lower in countries in the north-west of Europe compared with those in the south-east (Figure 1.6). The main causes of hepatocellular cancer are HBV and HCV infections and alcohol consumption. In all countries, mortality from hepatocellular cancer is higher in males than in females (ECDC, 2010). Although these data are not specific to people who inject drugs, they provide the scale of morbidity and mortality related to infectious liver disease, a large proportion of which is accounted for by infection acquired through injecting drugs.

FIGURE 1.6

Hepatocellular carcinoma-related mortality per 100 000 population (men)



Source: ECDC (2010).

Prevention of hepatitis C among people who inject drugs

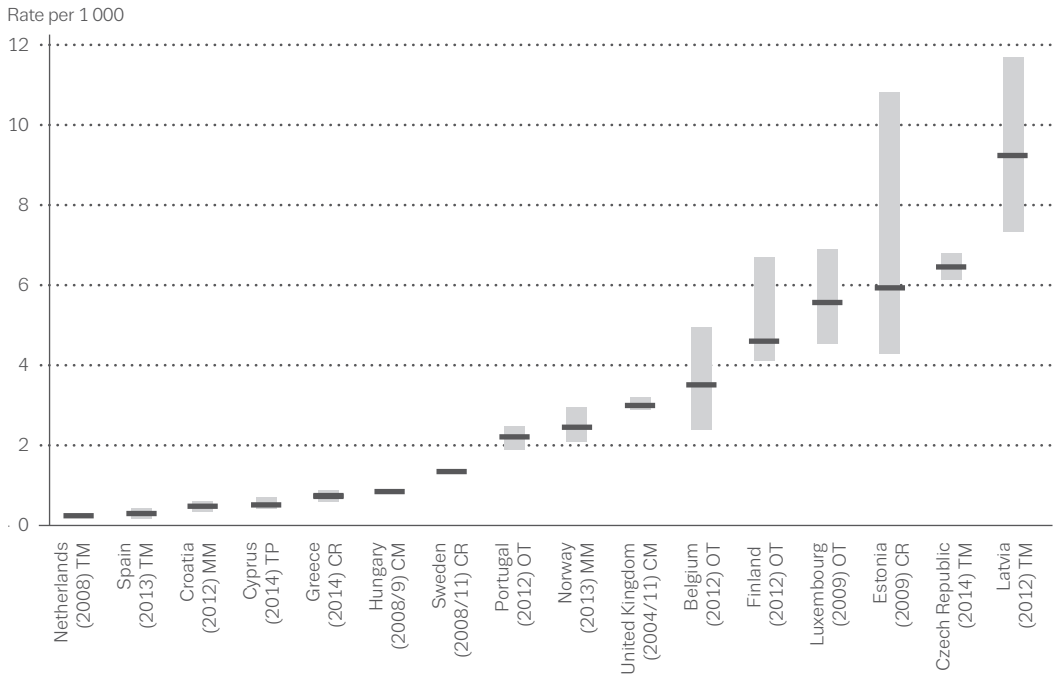
Modelling studies suggest that antiviral treatment could play an important and cost-effective role in preventing hepatitis C in people who inject drugs by reducing the number at risk of transmitting the virus (Martin et al., 2012; see also Chapter 4). These studies indicate that hepatitis C treatment may have a synergistic impact on prevention efforts, in particular when combined with the harm reduction interventions of opioid substitution treatment and needle and syringe programmes (Chapter 3). In this section we review the estimated prevalence of drug injecting and the coverage of opioid substitution treatment and needle and syringe programmes in Europe based on data from EMCDDA monitoring.

Estimated number of people who inject drugs

Relatively recent (2007–2014) estimates of the prevalence of drug injecting among the general population are available in only 16 of the 30 countries monitored by the EMCDDA (2016b). Estimated

FIGURE 1.7

Estimates of the prevalence of injecting drug use (rate per 1 000 population aged 15–64), 2007–14 data collection (last study available)



NB: Data displayed as point estimates and uncertainty intervals. Methods of estimation: CM, combined methods; CR, capture-recapture; HM, HIV multiplier; MM, mortality multiplier; OT, other methods; TM, treatment multiplier; TP, truncated Poisson.
Source: EMCDDA, 2016b.

prevalence varies strongly across countries: from less than 1 to up to 9 cases per 1 000 population aged 15 to 64 (Figure 1.7) and uncertainty intervals are often broad. Comparisons between countries using different methods and acquiring data from different sources should be made with caution. However, the magnitude of the differences and changes seen in estimates is generally confirmed by other data sources.

Based on the available estimates, the highest absolute numbers of current injectors are reported in the United Kingdom (122 900), the Czech Republic (45 600), Finland (15 600), Portugal (14 400), Latvia (12 600) and Spain (9 900). These numbers are important as they provide a proxy for the size of the group at potential risk of infection and transmission of the virus through injecting drug use. Combining estimates of injecting drug use with HCV prevalence estimates can enable us to understand the size and dynamic of the infection among this group.

Harm reduction measures targeting injecting drug use

In the European Union, harm reduction policies form an integrated part of the public health response to drug use-related health problems (Busch, 2013; Hedrich et al., 2008; Hedrich and Pirona, in press) and all countries implement opioid substitution treatment and needle and syringe programmes as core measures for the prevention and control of infections among people who inject drugs (EMCDDA, 2016a).

The degree to which the provision of these interventions meets the needs of the target population can be assessed by calculating some measure of coverage (Wiessing et al., 2009). For opioid substitution treatment, coverage is defined as the proportion of the target population (high-risk opioid users) receiving the intervention, whereas for specialised needle and syringe programmes it is number of units dispensed per head of the target population for this intervention (that is people who inject drugs). Not all countries are able to provide valid estimates of the size of these target populations. Coverage estimates can be calculated for 19 EU

Member States for substitution treatment and for 13 Member States for needle and syringe programmes. In some of these countries, there are considerable uncertainties associated with the estimates.

Needle and syringe provision

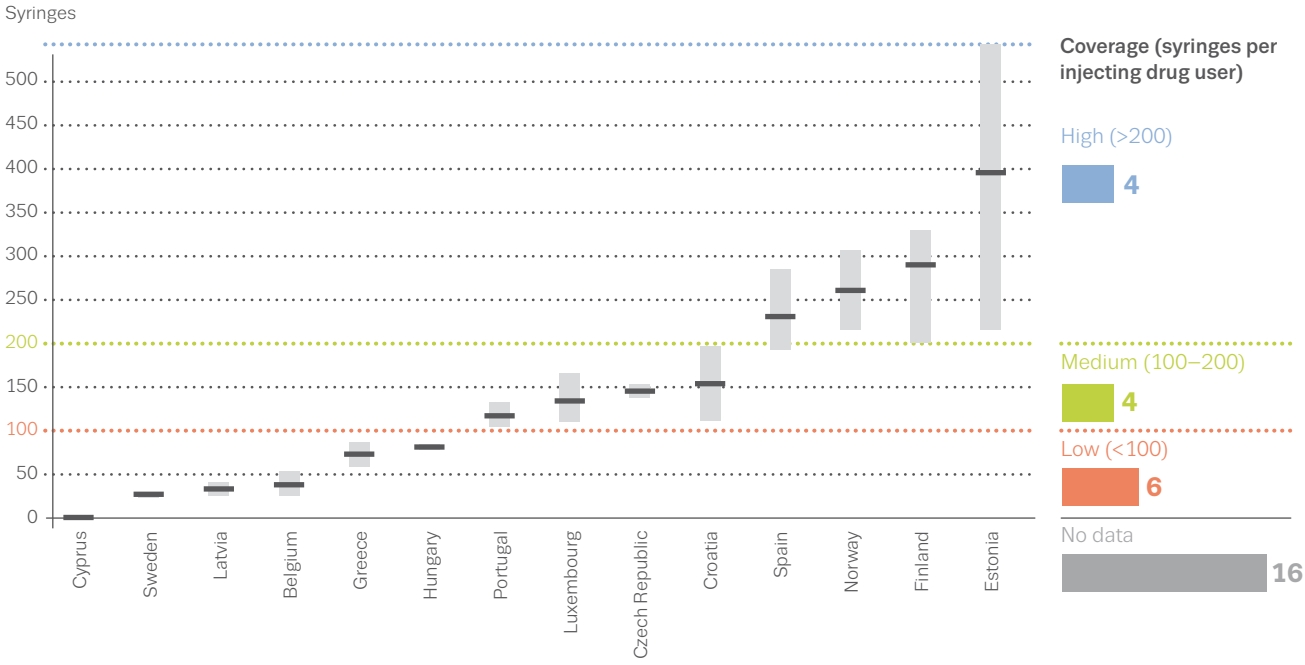
Initiatives to reduce the spread of infectious diseases through the sharing of syringes and other drug injecting equipment by providing sterile drug use equipment to people who inject drugs date back to the mid 1980s (Bunning et al., 1986; Hedrich et al., 2008). Needle and syringe programmes, integrated into multi-component harm reduction interventions, distribute tens of millions of syringes each year in Europe. In addition to sterile syringes and needles, a range of other injecting paraphernalia, including alcohol, pads, water, filters and mixing containers as well as equipment for inhaling drugs are distributed by harm reduction facilities in order to prevent bacterial and viral infections. The estimated number of syringes distributed each year per drug injector through specialised programmes — excluding syringes sold by pharmacies outside of such programmes — ranged from less than 50 in Cyprus, Sweden, Belgium and Latvia to more than 350 in Estonia (Figure 1.8). Comparing these estimates of syringe provision against international recommendations, less than a third of the countries that can be assessed provide syringes at a level judged to support effective harm reduction (at least 200 syringes per year per person who injects drugs; UNAIDS, 2012). It should be noted that the uncertainties around the estimates of size of the national drug-injecting population carry over into the estimates of coverage.

Opioid substitution treatment

Opioid substitution treatment is an effective measure to reduce the risk of transmission of infections and other drug-related harms among people who inject opioid drugs, particularly heroin (see Chapter 4). This intervention is targeted at high-risk opioid users, a population that, in addition to those injecting opioids, includes people using illicit opioids regularly or over a long period by other routes of administration. Overall, it is estimated that approximately one in two high-risk opioid users in Europe received substitution treatment in 2014 (EMCDDA, 2016a). This is the case for 10 of the 20 countries able to provide recent data allowing national coverage to be estimated. However, the available data indicate that in some countries less than 10 % of the estimated population of high-risk opioid users receive opioid substitution treatment (Figure 1.9).

FIGURE 1.8

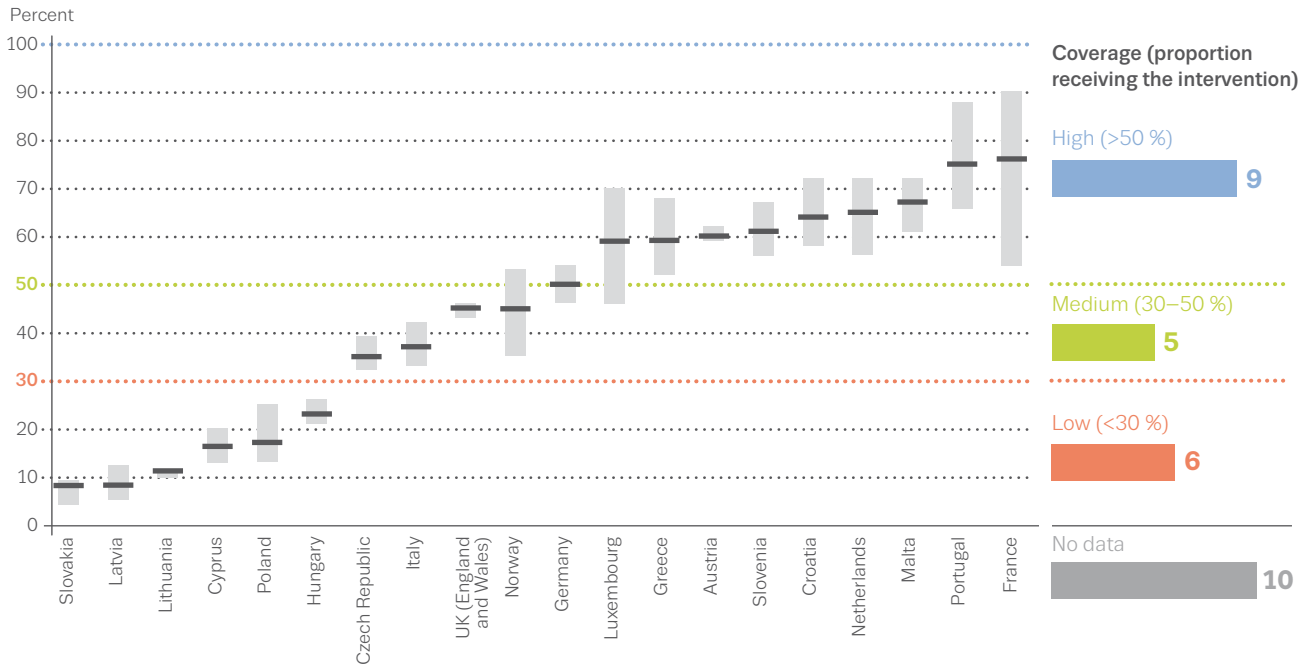
Number of syringes provided through specialised needle and syringe programmes per estimated drug injector in 2014 or latest available year



NB: Data displayed as point estimates and uncertainty intervals.

FIGURE 1.9

Percentage of the estimated population of high-risk opioid users receiving substitution treatment in 2014



NB: Based on population size estimates of opioid users (2007–2014), and number of people receiving opioid substitution treatment in 2014 (or most recent year available).

While improvements in screening and treatment are becoming a priority in new hepatitis C strategies in some countries, there is evidence that hepatitis C is not being addressed in a comprehensive manner, as several countries still show important gaps in prevention coverage, and HCV treatment provision to people who inject drugs continues to be reported as low.

Conclusion

The burden of hepatitis C is high in Europe and disproportionately affects people who inject drugs. In many countries more than half of those who inject drugs are infected. Current data indicate new infections and likely on-going transmission. The European picture is highly variable, with large variations in both the epidemiology of the infection and the prevention responses undertaken. The coverage of interventions in some countries continues to be low when measured against international standards and, in some instances, it has even been recently decreasing, significantly increasing the risk of HCV and other infections among people who inject drugs.

There are significant gaps and also general limitations in the available data on notifications, prevalence estimates, estimates of the numbers of people injecting drugs and coverage of the main prevention interventions. Serious gaps also exist in estimates of incidence, co-infection, genotypes, undiagnosed fraction, treatment entry and burden of diseases. All these are valuable indicators for monitoring the continuum of care, and they should be promoted and their availability improved in several countries where they are still underdeveloped.

In May 2016, the World Health Assembly adopted the first Global Health Sector Strategy (GHSS) on viral hepatitis, aimed at eliminating hepatitis B and C as public health threats (WHO, 2016). Against this background, and in the context of the on-going transformation of hepatitis C treatment, the current monitoring framework established by the EMCDDA together with the EU Member States and partner agencies needs to be further strengthened, and gaps to be filled, in order to support policymakers and public health planners to prioritise resources and tackle the epidemic.

Annex

TABLE A1

Anti-HCV sero-prevalence in the general population in the EU/EEA: summary of available evidence

EU Member States	Anti-HCV prevalence (%)	Year of study	Area	Sampling approach	Sample size
Belgium	0.1	2003	Regional	Random	1 834
	0.9	1993–4	Regional	Residual sera	4 055
Bulgaria	1.3	1999–2000	Regional	Random	2 211
Czech Republic	0.2	2001	National	Residual sera	2 950
France ([1])	1.3	1997	Regional	Sentinel GP convenience	11 804
Germany	0.4	1998	National	National health survey	6 748
	0.5	1997	Regional	Regional health survey	4 310
Greece	0.5	1997–8	Regional	Random	1 500
	1.3	1997	Regional	Household health survey	718
Italy	2.7	1996–7	National	Residual sera	3 577
	1.8–11.5	1983–2006	Regional	Random/convenience	721–3 884
Netherlands	0.6	2004	Regional	Random	1 364
	0.2	2006	Regional	Residual sera	2 200
Poland	1.9	1999	Regional	Convenience	2 561
Romania	3.5	2006–8	National	Sentinel GP random cluster	13 146
Spain	2.5	1996	Regional	Random	2 142
	1.6	1997–9	Regional	Random	1 170
Sweden	0.4	1991–4	Regional	Birth cohort convenience	5 533
United Kingdom	0.7	1996	Regional	Residual sera	6 401

NB: Countries with no available information are not presented in the table.
([1]) Another study was conducted in France in 2004 published in 2010, which found an estimate of overall anti-HCV prevalence of 0.84 % (95 % CI: 0.65–1.10). The HCV RNA prevalence estimates was 0.53 % (95 % CI: 0.40–0.70) (Meffre et al., 2010).
Source: ECDC (2010); Hahné et al. (2013).

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2

CHAPTER 2

Treatment of hepatitis C virus infection among people who inject drugs: uptake and outcome

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Introduction

Injection drug use is the main mode of hepatitis C virus (HCV) transmission in high-income countries, accounting for the majority of new and existing infections (Hajarizadeh et al., 2013). Efforts to tackle HCV infection in people who inject drugs are needed to reduce HCV-related morbidity and mortality, and prevent onward transmission of the virus (Grebely and Dore, 2011; Martin et al., 2011). Combination treatment with pegylated interferon (peginterferon) and ribavirin has been shown to achieve a sustained virological response in 46 to 52 % of cases of infection with HCV genotype 1 and 76 to 80 % of cases of infection with genotype 2 or 3, although these outcomes were reported in large clinical trials that excluded individuals with a recent history of drug use (Fried et al., 2002; Hadziyannis et al., 2004).

European guidelines have been recommending for some time that drug use should not exclude individuals from HCV treatment (EASL, 2015), but many services remain reluctant to treat people who inject drugs, citing concerns over adherence, increased susceptibility to side effects and the risk of reinfection through continuing to inject (Bruggmann and Litwin, 2013). This chapter evaluates and synthesises the available evidence relating to the uptake and outcomes of HCV treatment (including treatment adherence, sustained virological response, reinfection and morbidity related to liver disease) among people who inject drugs.

Methods

The chapter updates a previous systematic review (Aspinall et al., 2013) that considered treatment outcomes (i.e. sustained virological response, adherence and HCV reinfection) specifically among individuals who were injecting drugs during or after therapy. Further evidence sought for this chapter was evidence related to additional outcomes not included in the previous review: treatment uptake among people who inject drugs (evidence sourced from the individual studies already identified in the previous review) and the impact of sustained virological response on liver disease-related morbidity and mortality (evidence sourced from a recently published systematic review of the literature). Treatment uptake is defined as the proportion of individuals diagnosed as HCV RNA-positive in whom treatment for HCV infection was initiated during a period of 1 year. Liver disease-related morbidity was defined as the number or rate of diagnoses or hospitalisations for liver cirrhosis or hepatocellular carcinoma, and liver disease-related mortality was defined as the number or rate of deaths due to liver cirrhosis or hepatocellular carcinoma.

Systematic review

The MEDLINE, Embase and Cochrane databases were searched for primary articles examining HCV treatment with peginterferon and ribavirin among people who inject drugs and published between January 2002 and January 2014, thus updating the previously published systematic review by 2 years (Aspinall et al., 2013). Inclusion and exclusion criteria for the systematic review are outlined in Table 2.1.

There were very few studies examining the outcome of reinfection and, therefore, the inclusion criteria for this outcome were broadened to cover those who have ever used illicit drugs (rather than only those currently injecting drugs) and any treatment for chronic HCV (rather than only peginterferon and ribavirin).

TABLE 2.1

PICO (population, intervention, comparison and outcome) inclusion and exclusion criteria for the systematic review

Inclusion criteria	
Population	Study includes individuals who are HCV RNA-positive. Study includes those currently injecting drugs, here defined as either (i) injecting in the previous 6 months or (ii) described by the study authors as 'active' or 'current' injectors. The proportion of the study population currently injecting drugs is known.
Intervention	HCV treatment with peginterferon + ribavirin.
Comparison	Any or no comparison group.
Outcomes	Sustained virological response (the proportion of individuals by intention to treat in whom HCV RNA was undetectable for at least 24 weeks after completion of HCV treatment). Treatment adherence (80/80/80 adherence: the proportion of individuals by intention to treat who received 80 % of the peginterferon cumulative dose and 80 % of the ribavirin cumulative dose for 80 % of the time). HCV reinfection (the number of individuals who tested HCV RNA-positive following a sustained virological response per 100 person-years of follow-up).
Exclusion criteria	
	Studies were excluded if they stipulated a defined period of drug abstinence prior to starting treatment, even if this period was shorter than 6 months. For this reason, prison-based studies were excluded (as abstinence is a requirement in prison).

Articles that met the inclusion criteria were assessed for quality using the Newcastle–Ottawa Scale (Wells et al., 2014). Studies were assigned a score ranging from 1 (poor quality) to 9 (high quality). If more than one article reported on the same study, the article that provided the most comprehensive account of the study population was selected. Where appropriate, data were synthesised using meta-analysis.

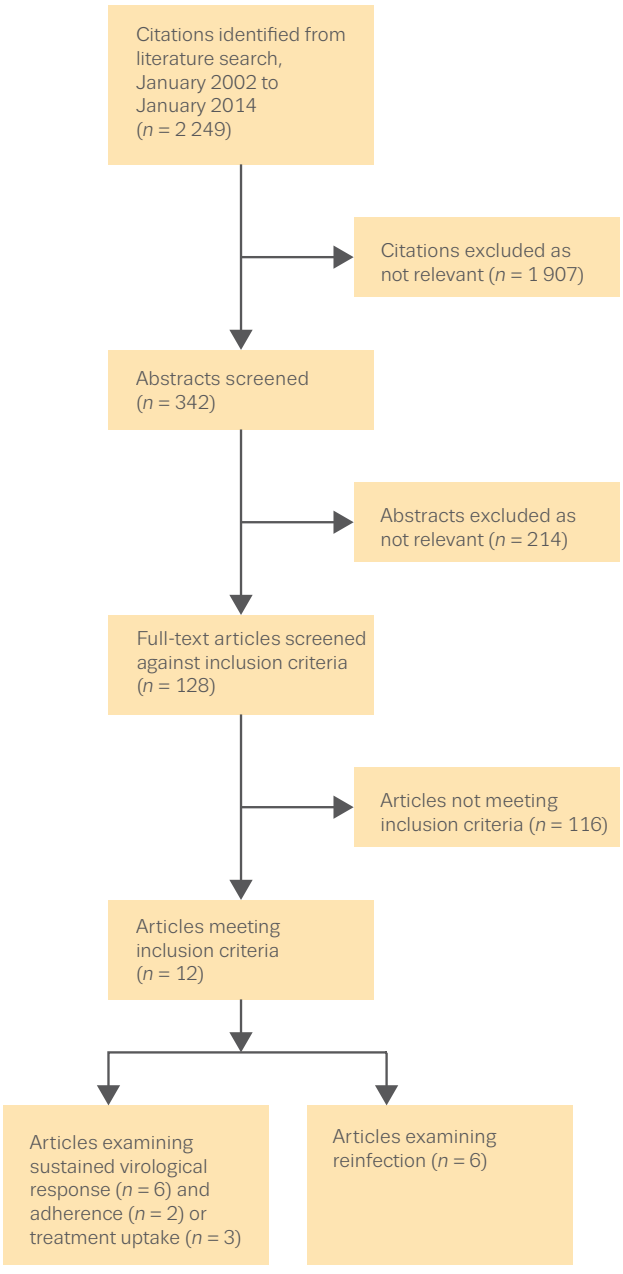
Data synthesis

Pooled outcome measures were synthesised for those outcomes (sustained virological response, adherence and reinfection) for which sufficient data were available. Sustained virological response and adherence and their exact 95 % confidence intervals (CIs) were calculated assuming a binomial distribution, and pooled estimates were derived using random effects methods. Subgroup meta-analyses were used to obtain pooled estimates of sustained virological response by injecting behaviour (all study participants versus those currently injecting) and HCV genotype (1 or 4 versus 2 or 3).

HCV reinfection rates were calculated per 100 person-years of follow-up, and exact 95 % confidence intervals were calculated assuming a Poisson distribution. Meta-analysis was undertaken using log-transformed incidence rates and corresponding log standard errors in a random effects model. Subgroup meta-analysis was used to calculate a pooled reinfection rate among those who injected drugs after having achieved a sustained virological response. All statistical analyses were undertaken using STATA 13 (StataCorp, College Station, TX, US).

FIGURE 2.1

Summary of systematic literature search of MEDLINE, Embase and Cochrane databases



Source: ECDC (2010).

Results and discussion

The results of the systematic literature search are shown in Figure 2.1. A total of 2 249 publications were identified, of which 342 abstracts and 128 full text articles were reviewed. In total, 12 articles (eight from Europe, two from Canada, one from the United States and one from Australia) met the inclusion criteria and were included in the review.

Treatment uptake

Three of the six studies that reported on sustained virological response (Table 2.2) also reported on HCV treatment uptake (Jack et al., 2008; Wilkinson et al., 2008; Lindenburg et al., 2011). The three studies included a total of 755 ever-users of illicit drugs, although the proportion who were current injectors was unknown. Participants were recruited from drug services or urban primary care services. Two studies offered in-house testing and referral to HCV services (Wilkinson et al., 2008; Lindenburg et al., 2011) and one study offered referral to a HCV specialist nurse (Jack et al., 2008).

Lindenburg et al. (2011) identified 196 HCV RNA-positive ever-users of illicit drugs, of whom 123 (63 %) completed a pre-treatment assessment and 58 (30 %) commenced HCV treatment over a period of 4.5 years (equating to an annual treatment uptake 6.6 %). Wilkinson et al. (2008) identified 441 HCV RNA-positive ever-users of illicit drugs, of whom 83 (19 %) attended for an assessment and 63 (14 %) commenced treatment over a period of 2 years (annual treatment uptake 7.1 %). Jack et al. (2008) identified 118 HCV RNA-positive ever-users of illicit drugs, of whom 86 (73 %) completed a pre-treatment assessment and 30 (25 %) commenced HCV treatment over a period of 2.9 years (annual treatment uptake 8.5 %). Pre-treatment assessments included standard assessment for HCV therapy (e.g. checking for medical or psychiatric contraindications to treatment) as well as an assessment of acute or unmanaged housing, financial or legal issues.

The annual treatment uptake figures quoted in these studies are higher than current population-based estimates of treatment uptake among both non- and ever-injectors: for example, annual treatment uptake among all individuals estimated to be chronically

TABLE 2.2
Uptake of HCV treatment among ever-users of illicit drugs

Reference, country	Setting	Reasons for not commencing treatment	Annual treatment uptake (%) (1)
Lindenburg et al. (2011), Netherlands	Drug users visiting drug services and primary care between January 2005 and July 2009 were offered testing and referral to in-house treatment	Of 196 HCV RNA-positive individuals identified: ▯ 45 (23 %) refused assessment, could not access treatment due to lack of health insurance or were lost to follow-up ▯ 28 (14 %) had still to complete assessments Of 123 individuals (63 %) who completed an assessment: ▯ 47 were not eligible for treatment (for medical, social or psychiatric reasons) or treatment was postponed because they had early infection with genotype 1 or 4 ▯ 76 were eligible for treatment but 18 refused (due to fear of therapy and side effects, co-morbidity, lost to follow-up or not known.) ▯ 58 started treatment	6.6
Jack (2008), United Kingdom	Two inner-city general practitioners offering opioid substitution treatment. Drug users attending drug services or primary care between February 2005 and January 2008 were offered referral to a HCV nurse	Of 118 HCV RNA-positive individuals identified: ▯ 32 (27 %) were not assessed because of loss to follow-up or death Of 86 individuals (73 %) who completed an assessment: ▯ 43 were not eligible for treatment (because of unstable housing, on-going excessive drug consumption, excess alcohol intake, significant mental illness or advanced liver disease) Of 43 individuals who were eligible for treatment: ▯ 13 had yet to start treatment at the time of the study ▯ 30 started treatment	8.5
Wilkinson et al. (2008), United Kingdom	Drug users attending a specialist addiction unit between March 2005 and March 2007 were offered in-house HCV testing and treatment	Of 441 HCV RNA-positive individuals identified: ▪ 358 (81 %) chose not to attend for assessment Of 83 (19 %) who chose to attend for assessment: ▪ 6 were not eligible for treatment Of 77 individuals who were eligible for treatment: ▪ 14 considered therapy but declined ▪ 63 started treatment	7.1

(1) Annual treatment initiations among ever-users of illicit drugs (including an unknown proportion of current injectors) who tested positive for HCV RNA.

TABLE 2.3

Characteristics and outcomes of studies examining peginterferon and ribavirin treatment for chronic HCV among people using drugs

Study characteristics		Participant characteristics							Intervention	Outcome		
Reference, country	Study design and recruitment	*n*	Mean age (years)	Male (%)	OST (%)	GT1/GT4 (%)	Stage	Definition of current injecting drug use (% of cohort)	Treatment setting, type of treatment, mode of delivery	80/80/80 adherence	Sustained virological response (%) by genotype	
											Ever-users	Current injectors
Jafferbhoy et al. (2012), United Kingdom	Retrospective cohort. Drug workers, prison nurses and other workers caring for drug users could test and refer drug users to HCV services	87	37	73	NA	36	3 % (1)	Intravenous drug use in the 12-month period before starting treatment (33 %)	Initially hospital-based, but evolved to nurse-led service in hospital and community. Drug support workers could attend appointments or provide generic support throughout treatment. Treatment with peginterferon α2a/α2b + ribavirin	NA	All: 47 GT1/4: 35 GT2/3: 54	–
Lindenburg et al. (2011), Netherlands	Prospective cohort. Drug users visiting drug services and primary care were offered testing and referral to in-house treatment	58	48	77	84	28	NA	Injection drug use in the 6-month period before starting treatment (19 %)	Community service with visiting specialists in hepatology, psychiatry, virology and addictions. Peginterferon was directly observed. Staff at methadone clinics provided support/monitored side effects. Treatment with peginterferon α2a/α2b + ribavirin	NA	All: 64 GT1/4: 38 GT2/3: 76	–
Sasadeusz et al. (2011), Australia	Prospective cohort. Recruitment of OST users who were attending for HCV treatment at four tertiary hospital treatment centres	53	38	79	100	42	27 % (2)	Injection drug use in the 6-month period before starting treatment (36 %)	Hospital-based. Treatment delivered in one of four tertiary hospital treatment centres. Treatment with peginterferon α2a + ribavirin	45 (85 %)	All: 57 GT1/4: 36 GT2/3: 71	GT1/4: 43 GT2/3: 75
Papadopoulos et al. (2010), Greece	Prospective cohort. Individuals attending a HCV treatment centre within a department of internal medicine who reported injecting drug use	48	38	87	NA	40	NA	'Active injection drug use' (100 %)	Hospital-based. Treatment delivered at a treatment centre for chronic HCV within a department of internal medicine. Treatment with peginterferon α2a/α2b + ribavirin	NA	All: 60	GT1/2/3: 60
Jack (2008), United Kingdom	Cohort. Two inner-city general practitioners offering OST. Drug users attending drug services or primary care were offered referral to a HCV nurse	21	NA	NA	NA	33	NA	'Active injection drug use' (100 %)	Community-based. Treatment in primary care by clinical nurse specialist under supervision of infectious diseases specialist. Treatment with peginterferon α2a/α2b + ribavirin	NA	All: 62	GT1/4: 43 GT2/3: 71
Wilkinson et al. (2008), United Kingdom	Retrospective cohort. Drug users attending a specialist addiction unit were offered in-house HCV testing and treatment	47	43	NA	NA	~45	NA	'Current' injection of heroin or crack (29 %)	Community-based. Treatment delivered by consultant hepatologist and specialist nurse at monthly outreach clinics in needle and syringe programmes or primary care. Treatment with peginterferon α2a + ribavirin	36 (77 %)	All: 53 GT1/4: 45 GT2/3: 56	–

(1) Cirrhosis.
(2) Grade 3–4 fibrosis.
OST, opioid substitution treatment; GT, genotype; NA, not available.

infected with HCV in the United Kingdom is currently around 3 % (Public Health England, 2013). However, the studies included in this review are likely to overestimate treatment uptake among people who inject drugs, given that study participants were involved in specialist and well-established treatment programmes. Figures from the Australian needle and syringe programme survey suggest that overall treatment uptake among people who inject drugs is likely to be much lower, at around 1.8–2.8 % (Iverson and Maher, 2013).

Sustained virological response and treatment adherence

Six studies reported on sustained virological response following peginterferon and ribavirin treatment (Table 2.3): no additional studies not included in the previous review (Aspinall et al., 2013) were identified. The six studies included a total of 314 ever-users of illicit drugs, of whom approximately 141 (45 %) were current injectors. Three studies provided community-based treatment (Jack et al., 2008; Wilkinson et al., 2008; Lindenburg, 2011), two studies provided hospital-based treatment (Papadopoulos et al., 2010; Sasadeusz et al., 2011) and one study initially provided hospital-based treatment but extended into the community as the service developed (Jafferbhoy et al., 2012). In two studies additional support was provided: in one study (Lindenburg et al., 2011), participants received directly observed peginterferon, and staff at methadone clinics offered support and monitored side effects; in another study (Jafferbhoy et al., 2012), drug workers were encouraged to attend HCV appointments and provide general support to participants.

Across six studies, pooled sustained virological response among ever-users of illicit drugs was 56 % (95 % CI 50–61 %), and across two studies 80/80/80 treatment adherence was 82 % (95 % CI 74–89 %). When sustained virological response was analysed by HCV genotype, the rate of sustained virological response was found to be 37 % (95 % CI 26–48 %) among those infected with HCV genotype 1 or 4 and 67 % (95 % CI 56–78 %) among those infected with genotype 2 or 3. Among current injectors, sustained virological response was 61 % (95 % CI 51–72 %) regardless of genotype (Table 2.4).

The quality of evidence for the sustained virological response outcome was assessed as low (because it derived from observational studies) and for the adherence outcome was assessed as very low (because it came from observational studies and because data were sparse).

The pooled estimates of sustained virological response appear to be slightly lower than those quoted by major clinical trials (46–52 % among those infected with HCV genotype 1 and 76–80 % in those infected with genotype 2 or 3) (Fried et al., 2002; Hadziyannis et al., 2004). However, across two 'real-world' studies among non- and ever-injectors undertaken outside clinical trials, sustained virological responses were similar to those reported here (see Figure 2.2): 37–39 % among those infected with HCV genotype 1 and 70 % among those infected with genotype 2 or 3 (Thomson et al., 2008; Innes et al., 2012). These findings support current guidelines (EASL, 2015) that decisions about treatment should be made independently of an individual's injecting status. However, it should be noted that the

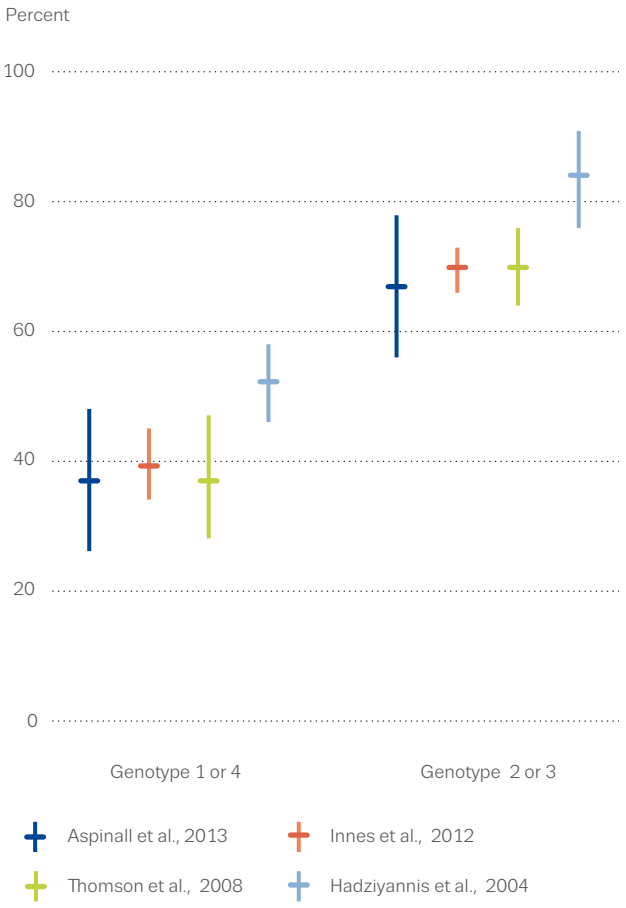
TABLE 2.4
Meta-analysis of studies examining HCV treatment outcomes among those currently and previously using drugs

Outcome	Inclusion criteria	Number of studies	Pooled estimate (95 % CI) (1)	Heterogeneity (I^2) (%)
Sustained virological response	All studies			
	All genotypes	6	55.9 % (50.4–61.3 %)	3
	Genotype 1 or 4	4	36.9 % (25.6–48.2 %)	0
	Genotype 2 or 3	4	67.1 % (55.9–78.3 %)	46
	Current injectors			
	All genotypes	3	61.4 % (51.2–71.5 %)	0
	Genotype 1 or 4	2	42.9 % (17.5–68.2 %)	0
	Genotype 2 or 3	2	73.1 % (55.2–91.0 %)	0
Reinfection	All studies	6	2.4 (1.0–5.9) per 100 person-years	0
	Individuals who reported injecting drugs after achieving sustained virological response	5	6.5 (2.5–16.9) per 100 person-years	0

(1) Random effects method used if $I^2 \geq 30$ %.

FIGURE 2.2

Comparison of HCV treatment outcomes (percent achieving sustained virological response) in published studies of pegylated interferon and ribavirin treatment



The study by Aspinall et al. (2013) is a meta-analysis of studies of people who inject drugs; participants in the other three studies were drug users, some of whom were ever-injectors — two (Innes et al., 2012; Thomson et al., 2012) are cohort studies and one (Hadziyannis et al., 2004) is a randomised controlled study. The last three studies were not included in the meta-analysis carried out by Aspinall et al. (2013) because they included non-injecting participants and an unknown proportion of current or former injectors.

participants who commenced treatment in these studies are likely to be a highly selected population, as treatment uptake after assessment was low. Therefore, the results of our review are likely to be based on a specific population of current injectors who are eligible and motivated to attend for assessment and treatment.

Although it was not possible to investigate other factors that may have impacted on treatment outcomes (because of the small number of studies and a lack of comparable data across studies), previous studies have suggested that lower social functioning (Dore et al., 2010) and a history of untreated depression (Alvarez-Uria et al., 2009) are associated with a lower chance of achieving a sustained virological response. An assessment of an individual's social circumstances and the availability of support should therefore be an important consideration in any decision about commencing HCV treatment.

The results reported here are limited to the small number of studies in which all or a known proportion of the study participants were current injectors, with the aim of providing more relevant information to clinicians managing this population group. Consequently, the data available were limited, with considerable uncertainty around each pooled outcome estimate. However, a review by Dimova et al. (2013) that used a wider definition of drug use (ever-use of illicit drugs, including injection use) reported similar pooled sustained virological responses to our review: 44.9 % (95 % CI 41.0–48.9 %) among those infected with genotype 1 or 4 and 70.0 % (95 % CI 62.9–76.3 %) among those infected with genotype 2 or 3.

Treatment adherence was relatively high in this review (82 %) compared with previous reports (McHutchison et al., 2002), although this estimate was derived from just two studies (involving a total of 100 patients). This difference may in part be explained by the varying definitions of adherence across studies, with some calculating on-treatment adherence (i.e. taking into consideration the number of missed doses while on therapy) and others cumulative adherence (i.e. taking into account early discontinuation of therapy) (Weiss et al., 2009). Greater standardisation of definitions of adherence is needed to allow more meaningful comparisons between studies in the future.

Reinfection

Six studies examined reinfection in individuals who had achieved a sustained virological response (Dalgard et al., 2002; Backmund et al., 2004; Currie et al., 2008; Grebely et al., 2010; Grady et al., 2012; Hilsden et al., 2013) (Table 2.5). Participants comprised a total of 162 people who had ever used illicit drugs, an unknown proportion of whom were current injectors at HCV treatment initiation. The total number of person-years of follow-up was 436.9 (range 36.0–131.6 person-years). Five studies reported the proportion of the study population that injected drugs after having achieved a sustained virological response and this ranged from 21 % to 50 %. HCV was treated with peginterferon and ribavirin (Hilsden et al., 2013), peginterferon/interferon and ribavirin (Grebely et al., 2010) or interferon with or without ribavirin (Dalgard, 2002; Backmund et al., 2004), or was not reported (Currie et al., 2008; Grady et al., 2012). Advice or counselling on reducing the risk of reinfection following treatment was offered in three studies (Backmund et al., 2004; Currie et al., 2008; Grebely et al., 2010).

TABLE 2.5

Characteristics and outcomes of studies examining HCV reinfection after achieving sustained virological response in ever-users of illicit drugs and current injectors

Study characteristics				Participant characteristics and study outcomes									
Reference, location	Study design	Recruitment and exclusion criteria	Treatment and risk reduction interventions	SVR (1)	Age at recruitment (years)	Male (%)	Injecting post SVR, *n* (%)	Lost to follow-up (%)	Reinfection (confirmed) (2)	Total follow-up (person-years)	Follow-up among those injecting post SVR (person-years)	Total reinfection rate (3)	Reinfection among those injecting post SVR (3)
Hilsden et al. (2013), Alberta and British Columbia, Canada	Randomised controlled trial	Current injection drug/crack cocaine users attending two inner-city health clinics serving the homeless and marginalised poor	Peginterferon α2a + ribavirin	31	NA	NA	NA	26	1 (0)	36.0	NA	2.78 (0.07–15.48)	NA
Grady et al. (2012), Amsterdam, the Netherlands	Prospective cohort	Illicit drug users who received HCV treatment through the Amsterdam Cohort Study of drug users	Peginterferon α2a/α2b + ribavirin delivered in a multi-disciplinary setting	42	51 (median)	74	11 (26)	NA	1 (1)	131.6	29.2	0.76 (0.02–4.23)	3.44 (0.09–19.15)
Grebely et al. (2010), Vancouver, Canada	Prospective cohort	Illicit drug users attending two community clinics offering addiction services. HCV treatment from visiting infectious disease specialists; 54 % injected drugs in the 6 months before HCV therapy	Ribavirin + peginterferon α2a/α2b or interferon α2b. Counselling on risk of reinfection	35	44 (mean)	86	16 (46)	11	2 (0)	62.5	37.7	3.20 (0.39–11.56)	5.31 (0.64–19.16)
Currie et al. (2008), San Francisco, US	Prospective cohort	Injecting drug users who were part of a larger longitudinal study that recruited by advertising at hospital entrances and in infectious diseases, liver and methadone clinics	'Antiviral treatment'. HCV and drug counselling	9	46 (mean)	89	2 (22)	NA	1 (0)	38.0	3.5	2.63 (0.07–14.66)	28.57 (0.72–159.19)
Backmund et al. (2004), Munich, Germany	Prospective cohort	Opiate-dependent injecting drug users receiving inpatient drug detoxification treatment were recruited to a study of HCV treatment	Interferon α2a ± ribavirin. Counselling on risk of reinfection	18	32 (median)	61	9 (50)	NA	2 (1)	50.8	23.8	3.94 (0.48–14.22)	8.40 (1.02–30.36)
Dalgard et al. (2002), Oslo, Norway	Prospective multicentre cohort	Individuals infected by injecting drug use were recruited to a trial of HCV treatment. Potential participants had to state that they had been abstinent for 6 months	Interferon α ± ribavirin	27	30 (median)	67	9 (33)	NA	1 (1)	118.0	40.0	0.85 (0.02–4.72)	2.50 (0.06–13.93)

(1) Number of individuals in cohort who achieved sustained virological response post treatment for HCV.
(2) Confirmed by genotyping or sequencing analysis.
(3) Per 100 person-years, (95 % confidence interval).
NA, not available.

Across the six studies, the pooled estimate of reinfection among ever-users of illicit drugs was 2.4 (95 % CI 1.0–5.9) per 100 person-years. Among those who reported injection drug use after having achieved a sustained virological response, the risk of HCV reinfection was 6.5 (95 % CI 2.5–16.9) per 100 person-years (five studies, 47 participants; see Figure 2.3 and Table 2.4). The quality of evidence for the reinfection outcome was assessed as very low because the evidence derived from observational studies and because the study population comprised ever-users of illicit drugs, rather than current injectors at treatment initiation.

The pooled risk of HCV reinfection among people who inject drugs was considerably lower than estimates of the risk of primary HCV infection among the same group (13.6 per 100 person-years (95 % CI 8.1–20.1) versus 25.0 per 100 person-years (95 % CI 20.2, 30.3) respectively) based on studies of users of needle and syringe programmes over comparable time periods (Grebely et al., 2014; Palmateer et al., 2014). However, the total number of person-years of observation across the six studies was low, creating considerable uncertainty around this estimate. Further, the inclusion of former drug users in the study population (for whom the risk of relapse to injecting drug use is likely to be lower), as well as exposure to specialised treatment and harm reduction programmes, may explain the lower rate of HCV (re-)infection observed here than typically found in drug-injecting populations.

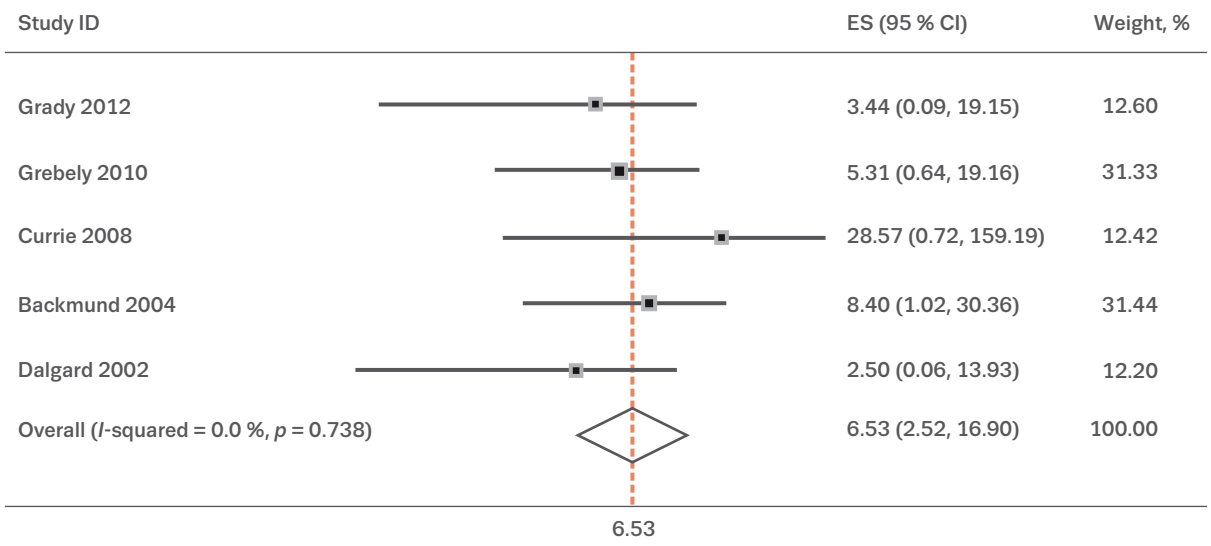
Reinfection risk was higher among those who reported injecting after having achieved a sustained virological response (although this finding was not statistically significant). Further work is needed to assist clinicians in identifying individuals who are at risk of resuming injecting, in order to allow appropriate harm reduction advice to be offered.

Impact of sustained virological response on liver disease-related morbidity and mortality

No studies have examined the impact of HCV treatment on liver disease-related morbidity and mortality specifically among ever-users of illicit drugs or those currently injecting. However, a recently published systematic review identified 19 cohort studies (involving both non- and ever-injectors) reporting the association between sustained virological response and mortality and hospitalisation-related morbidity (Chou et al., 2013). Notably, all 19 studies reported lower rates of adverse outcomes among participants who achieved sustained virological response than among those who did not. The adjusted hazard ratios for hepatocellular carcinoma ranged from 0.12 to 0.46 (equivalent to a 2.2- to 8.3-fold rate reduction). Similarly, adjusted hazard ratios for mortality due to liver disease ranged from 0.04 to 0.27 (i.e. a 3.7- to 25.0-fold rate reduction). Finally, adjusted hazard ratios for all-cause mortality ranged from 0.07 to 0.71 (i.e. a 1.4- to 14.3-fold rate reduction). In none of the studies was participation restricted to people who inject drugs,

FIGURE 2.3

Meta-analysis of HCV reinfection risk among people who reported injecting drugs after achieving a sustained virological response



NB: Weights are derived from random effects analysis.

but in one study, that of Innes et al. (2012), the majority of the participants were current or former injectors with liver fibrosis of any stage. An important finding from this study was that, although patients who achieved a sustained virological response indeed exhibited a reduced risk of hospitalisation for liver disease compared with their counterparts who failed to achieve a sustained response, their risk remained, nevertheless, 10.5 (range 8.7–12.9) times higher than that of the general population. The studies also over-represent individuals with advanced liver disease and under-represent those with milder disease. The inference that the benefit demonstrated in individuals with advanced fibrosis can be extrapolated to those with mild fibrosis needs more investigation. Further, none of the studies identified by Chou et al. (2013) collected comprehensive data on alcohol consumption and other lifestyle factors that may have confounded the relationship between exposure to HCV and adverse liver-related outcomes. It might be expected that such confounding would serve to over rather than under-estimate the benefit of a sustained virological response.

A recently published simulation model (Innes et al., 2014) quantified what patients stand to gain from sustained virological response; however, the analysis did not take account of the benefits of a potential reduction in onward transmission (see Chapter 4). What became apparent from this modelling exercise, and novel synthesis of the existing evidence base, is that some patients have far more than others to gain from a sustained virological response. For instance, in a currently injecting 30-year-old with mild fibrosis, the chance of a sustained virological response conferring additional life-years is 12.6 % (95 % CI 7.8–17.9 %) and the chance of a sustained virological response conferring additional healthy life-years is 16.6 % (95 % CI 10.5–23.0 %). For comparison, a sustained virological response holds a far greater attraction for a currently injecting 30-year-old with compensated cirrhosis, having a 54.5 % (95 % CI 42.9–65.4 %) chance of conferring additional life-years and a 64.0 % (95 % CI 50.9–75.0) chance of conferring additional healthy life-years. Thus, the impact of a sustained virological response is far more nuanced than the commonly applied 'sustained virological response = cure' heuristic (Brau, 2013) would suggest.

Conclusion

Treatment of HCV can result in acceptable outcomes in individuals who report current injecting drug use and who meet standard eligibility criteria for commencing HCV treatment. Owing to the small number of studies available, it was not possible to investigate other factors, such as the mode of treatment delivery and the availability of treatment support, that are likely to impact on treatment outcomes. Treatment decisions need to take account of each individual's social circumstances and the availability of support, as well as the anticipated clinical benefit of achieving a sustained virological response. The risk of HCV reinfection following achieving a sustained virological response was found to be relatively low, but there is considerable uncertainty around this estimate among those who continued to inject after achieving a sustained virological response. Further work is needed to assess the risk of HCV reinfection among people who are actively injecting illicit drugs, and it is likely that this risk can be accurately assessed only once treatment is scaled up and more equitably provided in this population.

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3

CHAPTER 3

Strategies to improve hepatitis C care and to enhance treatment uptake and adherence among people who inject drugs in Europe

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Interferon-free regimens for people who inject drugs

People who inject drugs generally have a negative view of interferon, and some physicians hesitate to prescribe this drug because they fear that it may have unacceptable side effects, such as those that resemble opioid withdrawal symptoms (Treloar et al., 2014). Mental health side effects are especially feared in this population, among which the prevalence of psychiatric disorders is high. In fact, the potential side effects of interferon are diverse and are usually easily managed; only in rare cases are they life-threatening. Parenteral application also presents a barrier to interferon use for many of those who inject drugs.

Interferon-free regimens for the treatment of hepatitis C are well tolerated; cure rates are over 95 % and in most cases treatment takes only 12 weeks (see Chapter 5). Clearly, this makes the delivery of hepatitis C care easier as exhaustive management of side effects will no longer be necessary. Nonetheless, adherence to treatment will remain an important issue not only because of the risk of resistance but also because of the cost of the treatment.

Interferon-free regimens are likely to overcome, at least to some extent, the reluctance of people who inject drugs to undergo treatment for hepatitis C, especially the reluctance based on fear of side effects and the complexity of application. However, the inability of people who inject drugs to access testing and treatment facilities and discrimination against injecting drug users will remain major barriers to care and, therefore, the need for specific settings and measures for this population will remain.

Local examples from Europe

While the following examples of need-adapted care settings for hepatitis care among people who inject drugs have been developed in the interferon era, the lessons they offer may also guide efforts to improve care provision for this patient group under interferon-free conditions.

Measures to improve case-finding and access to testing

Given the low rates of testing for hepatitis C virus (HCV) among people who inject drugs (Hagan et al., 2006; McDonald et al., 2010a), the first steps to improve care for those infected with the virus should focus on additional detection strategies accompanied by awareness programmes. People who inject drugs are most likely to be successfully tested in places where they are in contact with the health care system, for example in specialist drug treatment clinics, emergency departments (Stepanova et al., 2011) or general practices (Senn et al., 2009).

Participation in opioid substitution treatment programmes increases the probability of being tested. Test rates of more than 90 % have been reported among drug users undergoing treatment programmes at a general practice in Switzerland (Senn et al., 2009) and at a multidisciplinary addiction facility in the Netherlands (Lindenburg et al., 2011). Senn et al. (2009) demonstrated that a complete assessment, including identification of chronic hepatitis C (by testing for HCV RNA) and determination of HCV genotype, was feasible for 91 % of patients in opioid substitution treatment

programmes (*n* = 360 patients) treated by one office-based general practitioner (GP) in Switzerland (Senn et al., 2009). Slightly less favourable (but still impressive) results were obtained in another Swiss study comparing HCV antibody test rates among drug users receiving opioid substitution treatment under GP care and those treated in specialised addiction outpatient clinics (66 vs. 78 %) (Pelet et al., 2007). The lower test uptake among those being treated by GPs may be explained by the GPs' low case loads, which were associated with a lack of knowledge of HCV (Overbeck et al., 2011). Nonetheless, HCV test rates can be higher among individuals in opioid substitution programmes than in those less closely in contact with health care (Volk et al., 2009).

For these reasons, special efforts should be made to get people who inject drugs into opioid substitution treatment and to provide additional testing settings for this population. Low-threshold facilities can serve as an initial point of HCV testing, utilising point-of-care or non-invasive (such as dried blood spots) antibody tests. HCV testing in low-threshold facilities can also be used to monitor HCV prevalence among people who inject drugs in particular areas or regions. In addition, discussion of HCV and testing for the virus could be provided at facilities traditionally not offering health care services, such as shelters, consumption rooms or needle and syringe programmes (Zabransky et al., 2006). In Zurich, an on-going project offers rapid HCV antibody testing and discussion in combination with on-site liver transient elastography (a non-invasive ultrasound test of level of liver disease and cirrhosis) in consumption rooms (Bruggmann and Brunner, 2014). Anyone testing positive for HCV is referred for further assessment and needs-adapted hepatitis C care in specialised units in addiction clinics. This service is well accepted and widely used. In addition, earlier studies have shown that offering transient elastography examinations in low-threshold facilities has the potential to raise awareness of liver health and facilitate HCV testing and hepatitis C management (Foucher et al., 2009; Moessner et al., 2011).

In a systematic review, Jones et al. (2014a) found that the following factors may increase uptake of HCV testing: targeted case-finding; the provision of support and training for GPs; offering dried blood spot testing; and the provision of testing through outreach programmes. Dried blood testing is a non-invasive blood test, necessitating only a needle prick, that requires minimal training to undertake and is easy to conduct in people with poor venous access — so increasing opportunity for HCV testing in drug treatment centres and other facilities for people who inject drugs.

According to qualitative studies that have evaluated drug users' reasons for not getting tested for HCV (Swan et al., 2010; Jones et al., 2014b), some view hepatitis C as a harmless disease, since symptoms are not immediate, and some face other problems that are given higher priority. Fear of treatment side effects and of invasive tests are also contributing factors. Awareness and education campaigns, along with information on the on-going development of treatment options, are needed to allay such fears and counter misconceptions. This should be accompanied by continued efforts to make the testing process easier, with for example on-site HCV RNA or core antigen testing. As patients' perceptions of hepatitis C therapy are influenced mainly by peers, such campaigns should consider involving peers in both planning and implementation (as outlined in Chapter 6).

In many countries, prisoners constitute a considerable gap in the tested population (Arain et al., 2014), yet prisons, more than any other community site, provide an excellent opportunity to diagnose and treat a large number of people with chronic hepatitis C. Chapter 4 shows that hepatitis C case-finding in prison is dependent on uptake of treatment. We recommend that all prisoners should be offered an HCV test and the opportunity to discuss hepatitis C at the time of admission, and that, if they test positive and want to be treated, treatment should be made available to the same extent as offered in the community.

Measures to improve hepatitis C care

Access to, and uptake of, hepatitis C treatment is lower among people who inject drugs than in those who have contracted the disease in other ways. However, as shown in Chapter 2, it is possible to achieve rates of adherence and sustained virological response or cure in people who inject drugs that are similar to those seen in other groups — although a number of barriers at the patient, provider and system level have to be overcome before people who inject drugs can receive hepatitis C care (Bruggmann, 2012). Many of these obstacles can be overcome by taking specific measures as further outlined below.

Co-location of hepatitis C treatment with community/specialist drug treatment

A successful general approach that involves various measures and strategies is to take hepatitis C care to the people who inject drugs rather than waiting for them to show up in traditional care settings, which often are too rigidly structured to be attractive to such individuals.

According to Brunner et al. (2013), in Zurich, treatment of hepatitis C (with interferon- and ribavirin-based treatments) among people who inject drugs, many of whom have other illnesses and continue to use drugs, is most likely to be successful if it takes the form of integrated primary care-based multidisciplinary management under one roof. They reported an overall rate of sustained virological response of 62 %, including among individuals infected with all HCV genotypes and in some cases co-infected with HIV (human immunodeficiency virus), a rate comparable to that reported in studies of non-drug-using populations. Various supporting strategies, such as directly observed therapy, weekly consultations for psychosocial support and side effect management, peer involvement, and psychiatric and social care, were provided on an individual basis depending on needs.

In a GP-based model of hepatitis C and addiction care in Switzerland, Seidenberg et al. (2013) also achieved favourable treatment outcome rates, again even with interferon- and ribavirin-based treatments (overall sustained virological response rate: 71 %). A GP who has received additional training in both hepatitis C care and addiction medicine can establish a very efficient 'one-stop shop' service, providing various different disciplines in one place (Seidenberg et al., 2013).

A Scottish GP-based model involves a hepatitis clinical nurse specialist under the supervision of a secondary care-based infectious disease specialist. Patients are assessed by the clinical nurse specialist in the GP's office and treatment indication is then determined by an interdisciplinary team. Outcomes among patients receiving hepatitis C treatment in the GP surgery are comparable to those achieved in secondary care units (Jack et al., 2009).

In Prague, a programme of comprehensive care has been established with the goal of reaching people who inject drugs and offering timely and targeted health care services, including individually tailored hepatitis C therapy. The programme comprises low-threshold access to medical services, including primary and specialised health care (hepatology, psychiatry); testing for blood-borne and sexually transmitted diseases; pre- and post-test discussion; harm reduction services such as opioid substitution treatment; and psychosocial and crisis interventions. All medical and non-medical interventions are concentrated in one location. The programme is located in an outpatient health care centre that is also attended by non-drug users, preventing segregation of patients with 'stigmatising' disease. People who inject drugs share the experience with the programme through peer-to-peer networks supplemented by targeted information from outreach workers. In this setting, the overall rate of sustained virological response to hepatitis C treatment (pegylated interferon and ribavirin) is over 80 % (unpublished data).

In a community-based addiction unit in London attended by homeless people, patients with chronic hepatitis C who inject drugs are assessed by a hepatologist in collaboration with a nurse. When indicated, treatment is offered directly at the outreach clinic by a team consisting of the nurse and a psychiatrist. Evaluation found that treatment outcome is not affected by on-going alcohol or drug consumption (Wilkinson et al., 2009).

In a controlled multicentre trial in Germany, the effect of a series of planned psycho-education sessions on treatment retention and outcome was assessed (Reimer et al., 2013). Psycho-education was provided in weekly 1-hour group sessions covering topics such as HCV infection, hepatitis C disease course, treatment, side effects, coping strategies and the effective use of health care support. Sustained virological response rates and retention in treatment were positively influenced by psycho-education among patients with mental distress and those who required a longer course of treatment (i.e. those infected with HCV genotype 1 or 4). In addition, different forms of peer support models have been implemented successfully with benefits for hepatitis C assessment, treatment rates and adherence (Sylvestre and Clements, 2007; Grebely et al., 2010; Stein et al., 2012; Crawford and Bath, 2013), although most of these models were developed outside Europe.

A nationally coordinated approach encompassing a variety of different measures tailored to the individual needs of the different regions is necessary to effectively improve access to hepatitis C care. In the following section we highlight some key case studies.

National and regional coordinated examples in Europe: Scotland, France and Slovenia

The Scottish strategy to improve hepatitis C care for people who inject drugs

The Scottish strategy and national action plan to improve hepatitis C care acknowledges people who inject drugs as a key population among those affected by hepatitis C, but the national action plan also represents a comprehensive approach to hepatitis C at both the population and individual level. In this Scottish case study, the formation of the action plan will be reviewed

with emphasis on those strands relevant to people who inject drugs. In June 2004, Scotland's health minister recognised hepatitis C as one of the country's most challenging public health concerns (Chisholm, 2004). This was prompted by a Royal College of Physicians of Edinburgh (2004) consensus conference, which highlighted that 'services were struggling to cope with the burden of infection' and that 'significant resources needed to be directed at improving prevention and delivery of care'. Subsequently, Scotland's health minister and chief medical officer launched Scotland's hepatitis C action plan in September 2006 (Scottish Executive, 2006). Its aims were (i) to prevent the spread of HCV, particularly among people who inject drugs, (ii) to diagnose HCV-infected people, particularly those who would most benefit from treatment, and (iii) to ensure that those infected receive optimal treatment, care and support; with the overarching strategic aim of reducing the mortality and morbidity associated with HCV infection.

The plan had four phases:

- Phase I (2006–08) involved gathering evidence to inform proposals for the development of hepatitis C services.
- Phase II (2008–11) (Scottish Government, 2008), launched in May 2008, was a detailed plan of action with specified actions for responsible organisations to bring about a coherent and consistent approach to prevention, diagnosis, treatment and care of hepatitis C across Scotland, coupled with a performance-reporting structure that ensured that actions were carried forward.
- Phases III and IV (2011–20) (Scottish Government, 2011 and 2015) involved incorporating and 'mainstreaming' the hepatitis C action plan into a wider 'sexual health and blood borne virus framework', including reporting to central government on key performance indicators.

The HCV action plan, to be accepted by the clinical and non-clinical communities who would have to deliver it, needed to be based on the local epidemiology and an evidence base of best practice. Approaches adopted to generate the evidence involved analysis of existing data held on laboratory and clinical databases (Hutchinson et al., 2006), questionnaire surveys and face-to-face interviews with service providers, systematic reviews (Gilles et al., 2010; Palmateer et al., 2010), case-finding evaluations (Cullen et al., 2012), record linkage exercises (McDonald et al., 2010b) and modelling studies to estimate the impact of interventions in preventing infection and the burden of disease (Hutchinson et al., 2005).

By the mid-2000s, an estimated 50 000 Scots (1 % of the population) were living with HCV, and 75 % of these were chronic carriers (Hutchinson et al., 2006). Around 90 % of those infected acquired the virus through injecting drug use, and the majority remained undiagnosed (Hutchinson et al., 2006). It was estimated that only 20 % of those chronically infected had ever been in specialist care and only 5 % had received a course of antiviral therapy, while over 2 000 were living with cirrhosis and 1 000–1 500 injection drug users were being infected annually (Table 3.1) (Hutchinson et al., 2005). Thus, in a Scottish context, sharing of injecting equipment is the principal route of new infection and accounts for most prevalent infection. However, only a minority of people with chronic hepatitis C are current daily injectors, and a large proportion of those who inject or who recently have ceased injecting drugs are on opioid substitution treatment. Importantly, the action plan was based on the premise that everyone deserves therapy and that, as development of liver disease is not dependent on how infection is acquired, treatment services should focus on getting people who inject drugs into treatment and care.

For each action within the phase II plan, a desired outcome, performance measure and timescale were set out, and a lead organisation accountable for delivering the action and a network to support the lead organisation were identified. Generally, the actions were high level in nature (Table 3.1), allowing local National Health Service (NHS) boards the freedom to develop services in the context of their particular circumstances — taking account of existing arrangements for hepatitis C service provision and the epidemiology of infection in their area. Implementation involved representatives from all relevant disciplines and organisations, and took a graduated approach, focusing first on establishing the necessary infrastructures, prior to services being delivered and developed. National guidelines were developed to help ensure that approaches taken were effective, efficient and, where appropriate, consistent. Local and national networks were established so that experience, best practice and progress could be shared, and support, advice and guidance provided.

The first issue to address in any new disease area such as hepatitis C is to raise awareness (NHS Scotland, 2014) among both health care professionals and the general public. The majority of health care professionals are likely to have left formal education before the discovery or recognition of the significance of

TABLE 3.1

Summary of the key evidence, issues stemming from the evidence, actions designed to address the issues, progress made in delivering actions and associated outcomes, in the areas of testing, treatment, care and support

Key evidence and issues	Key actions (2008–11)	Outcomes
Key evidence (Scotland, mid-2000s) ▯ Over 60 % of people living with HCV remained undiagnosed. ▯ Only 20 % of chronically infected people had ever been in specialist care and only 5 % had been treated. Of 450 persons initiated on therapy each year, 4 % were prison inmates. ▯ Over 2 000 HCV-infected persons were living with cirrhosis, with over 100 developing liver failure each year. ▯ It was estimated that, if 2 000 persons per year received antiviral therapy over the next two decades, 5 200 cases of HCV-related cirrhosis would be prevented in the future. ▯ GPs and other service providers highlighted difficulties in taking blood from people who inject drugs as a barrier to HCV test uptake. **Major issues** ▯ The majority of people chronically infected with HCV remained undiagnosed and many of those diagnosed failed to reach and stay within specialist care services. ▯ Insufficient numbers of HCV-infected persons, including prisoners, were receiving antiviral therapy.	▯ NHS boards were required to have, or be affiliated to, a managed care network for HCV, comprising representatives of all stakeholder sectors. ▯ Testing/treatment services provided by NHS boards were expanded to increase numbers undergoing therapy in Scotland, from 450 per year to 1 500 in 2010/11 (since revised to 1 000 per year owing to financial restraints). ▯ Agreements between NHS boards and the Scottish Prison Service were developed to promote the treatment of HCV-infected inmates in prisons. ▯ Awareness-raising campaigns continued to be developed and implemented to meet the information needs of professionals and promote HCV testing among those at risk of being infected. ▯ A programme of work to evaluate approaches to HCV testing (e.g. dried blood spot testing) was undertaken.	▯ A public and professional website was launched (www.hepcscottland.co.uk), with further awareness campaigns in 2010. ▯ New approaches to getting people tested for HCV were implemented (e.g. dried blood spot testing). ▯ A 33 % rise in the annual number of new HCV diagnoses between 2003–08 and 2009–11 was achieved; 20 % of new diagnoses in 2011 were made in specialist drug services where dried blood spot testing had been introduced. ▯ Clinical services developed, leading to a doubling in the number of initiations of therapy (to 1 049 in 2010/11); 80 % of those starting treatment in 2010/11 were ever-injectors of drugs. ▯ The number of inmates started on therapy increased more than eightfold between 2007/08 (17) and 2010/11 (143).

hepatitis C, but without awareness of hepatitis C among the general public there will be no action and no drive to diagnosis.

This was achieved in Scotland by separate and staged awareness campaigns. The first was directed at health care professionals through the conventional routes of continuing professional development and education. Subsequently, the public was targeted through the media and multiple support organisations and patients groups. The key was to have reliable vetted sources of information available in a variety of formats to suit people who inject drugs; information appropriate for those with low literacy levels was particularly important, with verbal peer-to-peer dissemination of information also having a role.

The next issue to address was to convert awareness into greater levels of diagnosis. Guidelines were developed to determine who should be offered testing for HCV. This was combined with a wide range of action plan initiatives, and local and national networks played a key role in the promotion of hepatitis C testing. In one innovative development, test facilities were sited in high-prevalence environments. However, this alone is not enough to increase diagnosis rates among people who inject drugs, as facilities that offer testing are often located within conventional health care facilities and, to access such facilities, drug users must overcome a host of barriers. These include fears about stigma of drug use, fears of staff attitudes, accessing services in fixed pre-booked time slots and the difficulties of venepuncture in this client group.

The use of innovative technology, such as dried blood spot testing, combined with locating testing into non-clinical facilities, was a key development in increasing rates of diagnosis.

As a result of these actions, the number of new diagnoses of hepatitis C nationally has increased from around 1 500 per year to 2 000 per year, with testing in drug treatment services now accounting for around 20 % of all new diagnoses.

Furthermore, it is estimated that over half of all people in Scotland living with chronic hepatitis C have now been diagnosed. There is strong evidence that a real breakthrough has been made in getting people who inject drugs — particularly those in contact with harm reduction services — tested for HCV.

Diagnosing HCV infection is an important first step but is not effective or cost-effective unless it results in infected

individuals being treated for hepatitis C and cured. The action plan recognised that many of those diagnosed would be opioid-dependent and therefore mandated each regional managed care network to establish close links with drug addiction treatment services and to embed hepatitis C treatment services within them, or to establish clear and easy pathways into treatment.

This has been highly successful, and currently over 60 % of those entering hepatitis C therapy are also receiving opioid substitution treatment. Among this group rates of sustained virological response are similar to those achieved in former drug users or non-drug users (as highlighted in Chapter 2).

Over the 3-year period of phase II, annual initiations of antiviral therapy increased more than twofold among all infected individuals (of whom the vast majority had acquired infection through injecting drugs) and more than eightfold among infected prisoners, reaching 1 049 (involving 143 prisoners) in 2010/11, with these numbers being maintained at this level since then.

The national plan demonstrates that having a history of injecting drug use is no barrier to receiving, and indeed fully benefiting from, hepatitis C treatment.

Scotland's hepatitis C action plan is regarded globally as a model of good practice. It is evident that a considerable amount of progress has been made in improving hepatitis C prevention, diagnosis and treatment services. Much of the infrastructure, including networks and governance arrangements to ensure that hepatitis C is managed as a mainstream condition both within and outside NHS settings, has been embedded.

France

French policy for HIV prevention and care in people who inject drugs

For several years, until 1996, France experienced an unprecedented epidemic of HIV and HCV infection among people who inject drugs, with prevalence among this group reaching 40 % and 70 % respectively; in addition, approximately 500 overdose cases were reported annually (Emmanelli and Desenclos, 2005). Before then, access to needle and syringe programmes was possible but had not yet been scaled up and opioid substitution treatment was unavailable.

The health policy revolution for access to care and prevention for people who inject drugs started in 1996 with free and expanded access to antiretroviral therapy, opioid substitution treatment (buprenorphine in primary care and methadone in specialised centres) and needle and syringe programmes (Carrieri et al., 2006).

Needle and syringe programmes were mainly managed through special community centres for drug users ('reception and harm reduction support centres for drug users', abbreviated from the French to CAARUD), funded by the government. In addition to providing syringes and other harm reduction tools, these centres were tasked with providing education on reducing injecting and HIV and HCV risk behaviours and referring clients to HIV and HCV treatment, and to other services appropriate for this group (screening, vaccination, social groups for people who inject drugs, and infectious disease and psychiatric services).

A key component of the services was that — as far as possible — the same site was used as specialised centre for drug dependence (e.g. in the morning) and as a needle and syringe exchange site (e.g. in the afternoon). This double function turned out to be particularly appealing for people who inject drugs, who could rely on many services being available at the same site, that is a 'one-stop shop'.

During this period, the French health authorities were aware that they were aiming to control parenteral transmission of HIV (and HCV), but they did not realise they were also controlling sexual transmission of HIV among people who inject drugs by using antiretroviral treatment as prevention. The expanded access to buprenorphine and methadone in this population also was a means of ensuring long-term virological response (Roux et al., 2008, 2009), thus making this population 'less likely' to transmit HIV.

The high rate of opioid substitution treatment achieved in people who inject drugs (70–80 %), together with expanded access to needle and syringe programmes and control of HIV viraemia in the community, resulted in a striking reduction in HIV prevalence among this group of drug users. In 1995, people who inject drugs accounted for an estimated 28 % of patients diagnosed with acquired immunodeficiency syndrome (AIDS) (an acceptable proxy for new HIV diagnoses) (IVS, 1995); by 2012, people who inject drugs represented less than 1 % of new diagnoses of HIV infection (IVS, 2014).

France adopted a shared care model of prevention and care to meet the urgent need to control the HIV epidemic among people who inject drugs and also to place responsibility for prevention of HIV infection and care of opioid-dependent drug users on the primary care sector. The historical reasons behind this decision were that

French primary care physicians were already treating opioid dependence with palliative treatment (such as low-dose buprenorphine) and those offering care to people who inject drugs were already working in specialised networks, often linked to hospital HIV services or dedicated centres for care of dependent drug users. Primary care physicians became the main stakeholders advocating adequate care for opioid-dependent injection drug users (Des Jarlais, 2016), which in France was based particularly on buprenorphine because of its safety profile (Carrieri et al., 2006).

To summarise, French health policy compensated for the delay in providing access to comprehensive facilities for the prevention and treatment of HIV infection among people who inject drugs by rapidly scaling up harm reduction interventions at community sites and in specialised and primary care — which, in combination, significantly contributed to the control of HIV infection among people who inject drugs.

HCV among people who inject drugs in France: a difficult to manage public health imperative

The method of organising HIV prevention and treatment services could have been utilised to provide access to HCV prevention services and could have been particularly helpful in engaging people who inject drugs in hepatitis C treatment. However, 10 years after the French harm reduction policy was initiated, the prevalence of HCV infection had fallen only slightly (from 70 % to 60 %). Although data are incomplete, the evaluation of the last official government hepatitis plan (Haut Conseil de la santé Publique, 2013) clearly shows that people who inject drugs and migrants still have limited access to HCV screening. Moreover, in France HCV infection has been linked to the rising use of stimulants (crack cocaine) and cocaine, which, owing to its short half-life, if injected, needs to be injected several times per day. These data show the importance of increasing access to HCV screening, treatment and innovative prevention measures to address these new HCV risks (Aspinall et al., 2013).

Corroboration that controlling the spread of HCV infection in France by scaling up HCV treatment and strategies for HCV prevention (opioid substitution treatment and needle and syringe programmes) is likely to be difficult is provided by a recent mathematical model. The model projections suggest that hepatitis C treatment for prevention is likely to be more effective when the baseline prevalence in the targeted population is below 40 % (Martin et al., 2011), which is not yet the case in France.

In contrast, a recent study estimated the number of people who received pegylated interferon and ribavirin treatment in 2010 (Razavi et al., 2014) in 22 European countries using data supplied from a variety of sources. This was actually the last year when all European countries had access to a comparable regimen for treating hepatitis C. According to this study, France was the leading country, with the highest rates of treatment (Razavi et al., 2014). There are two possible reasons for this. First, hepatitis C is a major public health concern in France: based on death certificates, it is estimated that in France 2 600 deaths each year are attributable to complications of hepatitis C (cirrhosis or liver cancer) and 4 000 are attributable to HCV or hepatitis B virus (HBV) infection (IVS, 2008). Second, despite the issues raised above, access to HCV screening and treatment is better in France than in other European countries, as the French health insurance system allows even marginalised populations to have free access to care (Grignon et al., 2008).

Even though France was found to perform well in terms of HCV treatment rates, an evaluation of the national plan to combat hepatitis identified the decentralisation of health care at regional level as a major barrier to effective hepatitis C care and equity of access to it. Access to HCV screening relies on local initiatives and on the availability of regional funds specifically targeted at addressing hepatitis C and substance dependence. In non-urban areas, the absence of specialised centres for the treatment of substance dependence and of community prevention centres means that the responsibility for getting people who inject drugs living with HCV into treatment lies with primary care providers.

In effect, at the regional level, hepatitis C prevention and care may be incorporated in the general prevention plan and initiatives to implement it depend on the regional budget and regional priorities which depend on local political will. For example, the establishment of a supervised drug consumption room in the Paris area will be possible because this initiative is prioritised in the allocation of health resources, which was not the case in Marseille, though both cities have comparable HCV prevalence in people who use drugs. Such unwillingness on the part of local authorities is the main structural barrier to access to HCV prevention and explains the heterogeneity of policies across regions. In addition, other potential sources of access to hepatitis C care for people who inject drugs are less effective than community sites (CAARUD). Although community sites are particularly designed to attract marginalised people who inject drugs, some injection drug users may avoid attending CAARUD or specialised care sites for fear of stigmatisation, instead choosing to use their local

pharmacist, who in France can provide injecting equipment. Empowering pharmacists to refer people who inject drugs to hepatitis C screening and care could be an important initiative to capture individuals who remain outside the hepatitis C network of care.

Although 2012 data showed that HIV–HCV co-infected people who inject drugs enjoy the same rights to access treatment as other HCV patients (Salmon-Ceron et al., 2012), they were more likely to refuse hepatitis C treatment initiation because they fear pegylated interferon-related side effects (Broers et al., 2005), and particularly depressive symptoms and pain due to the hyperalgia that develops after prolonged exposure to opioids (Carrieri et al., 2007). The availability of direct-acting antiviral medicines, characterised by high sustained virological response rates and limited toxicity, is an opportunity to engage French people who inject drugs in HCV care and indirectly contribute to HCV prevention, provided that they can be prescribed in low-threshold sites and for any stage of liver disease. Given the high cost of these medicines people who inject drugs found it difficult to access treatment because the decision to treat was submitted to a multidisciplinary committee of health staff. However, the French ministry of health recently announced the universal access to direct-acting antiviral medicines and authorised community-based rapid HCV testing. These decisions will have major repercussions in engaging people who inject drugs in HCV care, provided that once they have been tested in low-threshold sites they can be referred to receive prompt HCV treatment in a comprehensive model of care.

Current initiatives aim to improve both prevention and treatment of hepatitis C among people who inject drugs:

- A community-based research project, the ANRS-AERLI study, has demonstrated the positive impact of an innovative intervention based on educational supervision of injection for people who inject drugs. It has shown a significant reduction of HCV risk practices and local complications at the injection site (Roux et al., 2016b) and an increase of access to HCV screening (Roux et al., 2016a). A scale-up of the AERLi intervention is envisaged following the application of the new French health law and this is expected to contribute to increasing access and provision of HCV prevention and screening to people who inject drugs.

- The diagnosis of liver fibrosis is aided by the availability of a non-invasive procedure to measure liver stiffness (transient elastography technology) in specialised centres for opioid dependence/community prevention centres (CAARUD) to monitor both fibrosis resulting from hepatitis and from alcohol consumption in people who are actively injecting drugs. The preliminary results from this national project, funded by MILDECA (Fédération Addiction, 2014), showed that repeated assessment of liver stiffness and counselling can help in reducing alcohol consumption and its liver-associated sequels.

- Relaxing the criteria for eligibility for treatment of hepatitis C with direct-acting antiviral medicines simplifies the clinical management of these patients so that hepatologist can share responsibility for care with infectious disease specialists (Karine Lacombe, Marseille, France, personal communication, 2015) or even primary care physicians.

- The presence of a hepatologist in centres for care of dependent drug users, or referral to a hepatologist, will increase access to hepatitis C treatment for people who inject drugs.

- Providing hepatitis C screening (rapid testing) and treatment to the most marginalised sectors using mobile units (e.g. buses by Médecins du Monde) and providing a package of services including transient elastrogaphy monitoring, treatment education and hepatitis C care are approaches that are particularly effective in difficult-to-reach populations (Bruggmann, 2012).

A priority in France is to increase access to HCV testing. Rapid on-site testing for HIV and HCV (Bruggmann and Litwin, 2013) has yielded promising results in France and should be considered by other countries. It is important to note that people who inject drugs, once cured, are at risk of HCV reinfection, so HCV prevention needs to continue in the community. The French National Agency for Research on AIDS and Viral Hepatitis is now focused on developing treatments for stimulant dependence and medically assisted injectable treatments, evaluating alternative standardised educational approaches to reduce the risk related to injection, increasing access to methadone through primary care and developing harm reduction interventions for crack users (ANRS, no date).

Hepatitis C prevention and care in French prisons

Imprisonment is an important environmental factor facilitating HCV infection but also potentially an opportunity to provide treatment for hepatitis C. A recent survey among the prison population based on medical records (which were available for 70 % of the potential study group) found that the prevalence of HCV infection

was 4.8 % (95 % CI 3.53–6.50 %), with injection drug users accounting for 70 % of HCV-positive inmates; of those infected, half were classified as 'viraemic' (Semaille et al., 2013). Currently, overall, only one in five prisoners is tested for HCV, and this takes place at the time of entry, that is at a time when prisoners are concerned more with their loss of freedom than with their health, something that was identified as a major limitation of the French government's hepatitis plan during its evaluation. Renewing the offer of hepatitis C testing during a prison stay may increase uptake of HCV testing and detection of individuals living with HCV. The evaluation also found that access to a specialist in infectious diseases or hepatology depends on the size of the prison, that only half of inmates testing HCV-positive are investigated for the presence of a chronic infection and that fibrosis assessment in prison settings is highly heterogeneous, complicating the decision to start hepatitis C treatment (Chiron et al., 2013). Further, although access to HCV screening for people who inject drugs seems to be poorer in prison than in the community, access to HCV prevention tools in prison settings is even more limited, as demonstrated by the PRI^{2}DE study (Michel et al., 2011).

In summary, although France is regarded as an example of good practice in the access to hepatitis C treatment it offers to those chronically infected with HCV, there remains room for improvement; in particular, approaches to hepatitis C screening for people who inject drugs are still far from ideal. New guidelines for care in prison are helping to change and standardise practices, but a novel national strategy for prevention and treatment of hepatitis in French prisons is urgently needed to ensure the principle of equity of access to health care among prisoners and the general population in France.

The Slovenian model of care

Among a population of 2 million in Slovenia, approximately 10 000 people inject drugs, with an estimated HCV seroprevalence rate of 27.3 % (the third lowest in Europe) (Drev, 2014). HIV and HCV co-infection is also extremely rare, as the rate of HIV seroprevalence among people who inject drugs is low, being consistently under 1 %. For example, during 2008–2012 only three individuals with anti-HIV antibodies were detected during unlinked anonymous testing of people who inject drugs for surveillance purposes (n = 947) and only one new HIV diagnosis was reported among this group of drug users (Drev, 2014).

In 1995, 18 Centres for the Prevention and Treatment of Drug Addiction (CPTDAs) were founded, managing approximately 4 500 people who inject drugs yearly, three-quarters of whom receive opioid substitution treatment (Kastelic and Kostapfel, 2010). The CPTDAs provide HCV testing to people who inject drugs entering the programme, and offer regular testing for 6–12 months for those testing negative. In the first national study evaluating the hepatitis C treatment rate among people who inject drugs managed by the 18 CPTDAs in 2006, the prevalence of HCV RNA among 1 450 people who inject drugs was 15.6 %, but only 3 % of those infected had received hepatitis C treatment by the time of the study (Maticic, 2014). The low treatment rate among HCV-positive people who inject drugs led to an urgent call for action.

Hepatitis C treatment in Slovenia is mostly delivered by infectious disease specialists at five hospital-based clinics. This is fully funded by the health insurance system with no limitations except that treatment must be prescribed by approved infectious disease specialists (and hepatologists in the case of advanced liver disease) in accordance with the guidelines established by the National Viral Hepatitis Expert Group in 1997. These guidelines do not exclude people who inject drugs from hepatitis C treatment (Maticic et al., 1999). In 2007, a national multidisciplinary health care network for the treatment of HCV infection in people who inject drugs was established, regionally integrating the existing medical settings of the 18 CPTDAs and five specialised clinics for treatment of viral hepatitis. The multidisciplinary network team includes clinical care providers (addiction therapists and infectious disease specialists), psychiatrists and counsellors (nurses, social workers) who have undergone additional medical education and training, and peers (formerly HCV-positive injection drugs user) and other supportive systems (such as family, friends, co-workers).

Since 2006, close collaboration among all health care workers involved in the management of hepatitis C has been encouraged in the form of attendance at annual national conferences. These conferences, in addition to promoting knowledge sharing among health workers and providing a forum for updating guidelines for the management HCV of infection in people who inject drugs, provide a valuable opportunity to exchange experiences. The national conferences played a crucial role in the development of an integrated approach for the management of HCV infection in people who inject drugs and continue to play an important role in maintaining this integrated approach. It was a result of the national conference in 2006 that national consensus guidelines for the management of HCV infection in drug users were developed in 2007 (Maticic and Kastelic, 2009). These outline procedures for the complex

management of HCV-infected people who inject drugs, including improved screening for those who are eligible for hepatitis C treatment; the provision of education, discussion and motivation-enhancing techniques individually tailored by highly qualified addiction therapists; and referral to infectious disease specialists for the treatment of hepatitis C in accordance with the best standard of care.

The guidelines for the care of patients with hepatitis C specify that each patient should receive a detailed and individualised hepatitis C treatment plan. In addition, treatment should be optimised, with side effects being aggressively managed and individually tailored interventions (e.g. a change in methadone dosage; addition of psychotherapeutics due to psychiatric comorbidities; additional motivation for adherence to treatment) performed at least monthly and in close cooperation with an addiction therapist throughout the treatment period. A standardised report on the patient's current medical and addiction/psychological condition is exchanged monthly between the hepatitis C and drug treatment specialists. This system enables hepatitis C and drug use, which are treated in separate medical settings, albeit in close proximity, to be managed in the most effective and rational manner, making use of facilities already existing in the country. The close liaison between the hepatitis C treatment specialist and the drug treatment therapist, and the active cooperation of the patient with both of them before and during hepatitis C treatment, also plays a crucial role in managing HCV infection in people who inject drugs.

As a result of these initiatives, among all the patients treated for hepatitis C in Slovenia the proportion of those who reported injecting drug increased from 5 % in 1997–99 to 16 % in 1999–2001, and to 36 % in 2002–04 (Brinovec et al., 2002, 2004; Maticic, 2014). However, since the introduction of the national multidisciplinary health care network in 2007, the share of injection drug users treated for hepatitis C has increased even further, reaching 78 % during the period 2008–10 (Maticic et al., 2013; Maticic, 2014). In addition, the proportion of injection drug users infected with HCV and treated for hepatitis C in CPTDAs increased from 3 % in 2006 to 13 % in 2010 (Maticic et al., 2013). Among those treated, a treatment adherence rate of 95.7 % and an overall sustained virological response rate of 82 % in the period 2008–10 have been accompanied by a marked improvement in certain lifestyle variables and a major decrease in drug use and opioid substitution treatment, which in combination justify the use of the multidisciplinary network model in Slovenia (Maticic et al., 2013, 2014).

In the era of highly effective interferon-free HCV treatment regimens, national clinical guidelines indicate direct-acting antivirals to be used on the basis of fibrosis stage, extrahepatic manifestations and co-morbidities and do not rule out people who inject drugs. Even though being safe and patient-friendly, direct-acting antivirals are prescribed in a multidisciplinary network under the same regimen as interferon-based treatment options. Aside from sustained virological response, some socio-demographic and behavioural benefits of successful treatment may play a crucial role in the future management of HCV infection in people who inject drugs, strongly influencing decision-makers towards even wider inclusion of injecting drug users in treatment for hepatitis C.

Conclusions

Treatment of hepatitis C among people who inject drugs must be specifically adapted to the needs of this marginalised population. According to currently available evidence and experience from national strategies, hepatitis C care should be integrated into existing addiction units if it is to reach people who inject drugs. New hepatitis C treatment regimens that are easy to administer and well tolerated will make it easier in the future to deliver comprehensive, multidisciplinary care to people who inject drugs. Specific measures to enhance engagement with testing and treatment and to support adherence delivered at primary care/community level will still be needed. Examples of good practice from different countries show that there is no single solution to close the gaps, and that even countries with good national plans have room for improvement, as exemplified by the case of France. Activities to improve hepatitis C care among people who inject drugs must be extended to prisons. Close collaboration between all professionals involved in care underpins every successful model of care. Primary prevention strategies — opioid substitution treatment and needle and syringe programmes — remain important and will need to be scaled up in some sites in order to maintain low HCV incidence and minimise the risk of reinfection.

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4

CHAPTER 4

Hepatitis C prevention among people who inject drugs: role and impact of hepatitis C treatment, opioid substitution treatment and needle and syringe programmes

Natasha K. Martin, Matthew Hickman and Peter Vickerman

Introduction and overview

There is increasingly strong evidence that traditional primary prevention measures such as opioid substitution treatment and needle and syringe programmes may be effective at preventing hepatitis C virus (HCV) transmission. However, modelling projections have shown that achieving substantial reductions in HCV prevalence among people who inject drugs requires HCV treatment. Antiviral treatment for hepatitis C is available and effective at curing a majority of individuals. A range of medications exist that are judged to be cost-effective in European settings — that is, the cost of treatment is lower than the amount that it is generally accepted that society is willing to pay for the additional years of healthy life that treatment will provide. These medications include pegylated interferon and ribavirin (NICE, 2004, 2006; Sroczynski et al., 2010), as well as newer, direct-acting antiviral therapies (Cammà et al., 2012; NICE, 2012a,b, 2015; Cure et al, 2015a,b). In addition to individual benefits, model projections have shown that HCV treatment for people who inject drugs could be an effective and cost-effective means of prevention in settings where chronic HCV prevalence among this group is less than 60 %; and that those who inject drugs should be prioritised after treating people with severe liver disease (Martin et al., 2011a, 2012, 2013a,b, 2016a,b). In most European countries, it will be essential to scale up hepatitis C treatment if the increasing trend in the prevalence of end-stage liver disease is to be reversed (Harris et al., 2014; Razavi et al., 2014). However, targeting people with cirrhosis, as is the priority in many European countries, is unlikely to lead to substantial reductions in hepatitis C virus transmission or the prevalence of HCV infection among people who inject drugs (Innes et al., 2014; Harris et al., 2016) as by the time cirrhosis has developed injecting drug use behaviour has usually ceased. Although much of the HCV treatment as prevention modelling work has been done in a few countries (Australia, Canada, France, United Kingdom), the scenarios reflect the situation in many European cities and, therefore, can be generalised. There is a need now to generate empirical data and conduct evaluations of the impact and cost-effectiveness of scaling up HCV treatment among people who inject drugs in European settings. In this chapter we discuss the empirical evidence and mathematical modelling work regarding HCV prevention interventions (harm reduction and hepatitis C treatment) among people who inject drugs.

Epidemiology of hepatitis C primary prevention

Epidemiological evidence indicates that traditional primary prevention measures such as opioid substitution treatment and needle and syringe programmes are effective in reducing self-reported syringe sharing. Both of these interventions can reduce transmission of human immunodeficiency virus (HIV), and evidence is emerging that they can also reduce transmission of HCV, in particular among those exposed to opioid substitution treatment and high-coverage needle and syringe programmes ([2]) in combination (Van Den Berg et al., 2007; Hagan et al., 2011; Turner et al.,

([2]) High-coverage needle and syringe programmes are those providing clients with at least one sterile syringe for each reported injection.

2011). However, it is unlikely that either intervention alone can reduce hepatitis C to negligible levels among people who inject drugs.

A study of 714 ever-injectors who were part of the Amsterdam Cohort Study, published in 2007, found that 'full harm reduction' (defined as consumption of at least 60 mg methadone daily in the past 6 months and no injecting drug use in that period; or consumption of at least 60 mg methadone daily, injecting drug use in the past 6 months, and all needles used in that period obtained via needle and syringe programmes) was associated with a relative risk of HCV acquisition of 0.36 (95 % confidence interval (CI) 0.13–1.03) compared with no harm reduction (Van Den Berg et al., 2007). However, one recent review and meta-analysis (Hagan et al., 2011) found that exposure to needle and syringe programmes was associated with a higher risk of HCV acquisition (1.62, 95 % CI 1.04–2.52) than no exposure to the intervention, though being on opioid substitution treatment was associated with a lower risk of HCV acquisition (0.6, 95 % CI 0.35–1.03).

A pooled meta-analysis from six UK sites involving 2 986 people who inject drugs investigated the association between opioid substitution treatment and high-coverage needle and syringe programmes (providing at least one sterile syringe per injection) and HCV incidence (Table 4.1). Turner et al. (2011) found that being on opioid substitution treatment was associated with a 59 % reduced risk of acquiring HCV (adjusted odds ratio (AOR) 0.41, 95 % CI 0.21–0.82), and participation in high-coverage needle and syringe programmes was associated with a 52 % reduction in risk (AOR 0.48, 95 % CI 0.25–0.93). Full harm reduction (the combination of the two interventions) was associated with approximately an 80 % reduction in HCV acquisition risk (AOR 0.21, 95 % CI 0.08–0.52).

Recently, there has been a further strengthening of the evidence base from non-European countries, with results from the Vancouver Injecting Drug Use Study in Canada (Nolan et al., 2014) and two other prospective studies of people who inject drugs, one in Australia (White et al., 2014) and one in San Francisco in the United States (Tsui et al., 2014), all of which reported that opioid substitution treatment can reduce the risk of HCV acquisition by 50 % to 80 % (Vancouver: AOR 0.47, 95 % CI 0.29–0.76; Australia: AOR 0.18, 95 % CI 0.04–0.77; San Francisco, AOR 0.39, 95 % CI 0.18–0.87).

A global systematic review on the individual and combined effects of opioid substitution treatment and needle and syringe programmes on the epidemiology of HCV among people who inject drugs is underway (Platt et al., 2016) and urgently needed. Similar systemic reviews have been performed for the impact of opioid substitution treatment (MacArthur et al., 2012) and needle and syringe programmes (Aspinall et al., 2014) on the incidence of HIV infection.

Model projections of impact of scale-up of full prevention

A number of mathematical modelling studies have considered the impact of a reduction in syringe sharing (Murray et al., 2003; Vickerman et al., 2007, 2009) or in the overall level of transmission risk (de Vos et al., 2012; Vickerman et al., 2012b, 2013) on the overall dynamics of hepatitis C epidemics among people who inject drugs. These analyses suggest that syringe sharing has to fall to very low levels (<1 syringe shared per month) before large reductions in HCV infection prevalence or incidence are achieved. In addition, a number of analyses, carried out in Australia, the Netherlands and the United Kingdom, have considered the impact or cost-effectiveness of opioid substitution treatment or needle and syringe programmes on HCV transmission. A modelling analysis of the Amsterdam injecting drug use cohort (de Vos et al., 2013) indicated that the scaling up of harm reduction was required to reproduce the full observed declines in HIV and HCV incidence, but a large proportion of the decrease may be due to changes in the population of injecting drug users. The analyses from Australia (Australian Government Department of Health and Aged Care, 2009; Kwon et al., 2009, 2012) used data on the dose–response relationship between syringe distribution and syringe sharing to assess how reductions in syringe distribution would affect syringe sharing and HCV transmission. The results suggested that current levels of syringe distribution are cost-effective in reducing HIV and HCV transmission (Kwon et al., 2012). No equivalent data are available for Europe — but the relationship is likely to be similar.

Finally, an analysis from the United Kingdom used recently published effect estimates of the extent to which opioid substitution treatment and current high-coverage needle and syringe programmes reduce the risk of HCV acquisition to show that scaling-up of harm reduction interventions in the United Kingdom has prevented HCV infections. The United Kingdom is among several European countries that, in the past decade, have achieved very high levels of opioid substitution treatment and needle and syringe programmes coverage (in the United Kingdom reaching approximately half of the drug-injecting population). Modelling indicates that without this high level of harm reduction coverage, the

TABLE 4.1
Relationship between intervention coverage and the incidence of new HCV infection

	Acquired HCV infection								
Intervention coverage	**No (*n*)**	**Yes (*n*)**	**%**	**Unadjusted odds ratio**	**95 % CI**	***P***	**Adjusted odds ratio**	**95 % CI**	***P***
Opioid substitution treatment (OST)									
On OST (1)	526	14	2.6	0.36	0.19–0.70	0.003	0.41	0.21–0.82	0.01
Not on OST	353	26	6.9	Ref.	–	–	Ref.	–	–
Needle and syringe programme (NSP) (2)									
≥ 100 % coverage	539	21	3.8	0.52	0.28–0.99	0.045	0.48	0.24–0.93	0.03
< 100 % coverage	254	19	7.0	Ref.	–	–	Ref.	–	–
Combined OST and NSP									
Full harm reduction: ≥ 100 % coverage, on OST (1)	392	8	2.0	0.19	0.08–0.47	<0.001	0.21	0.08–0.52	0.001
≥ 100 % coverage, not on OST	233	13	5.3	0.52	0.23–1.15	0.10	0.50	0.22–1.12	0.09
< 100 % coverage, not on OST (1)	134	6	4.3	0.41	0.15–1.12	0.08	0.48	0.17–1.33	0.16
Minimal harm reduction: < 100 % coverage, not on OST	120	13	9.8	Ref.	–	–	Ref.	–	–
Covariates									
						Gender	2.1	1.04–4.34	0.039
						Injection duration	1.0	0.44–2.07	0.906
						Crack injection	1.9	0.99–3.78	0.054
						Homelessness	2.9	1.41–5.97	0.004

(1) Logistic regression was used to calculate unadjusted and adjusted odds ratios (adjusted for the following covariates: female sex, homelessness in last year, injected crack in last month, duration injecting < 2.5 years) with probability (*P*) values and 95 % confidence intervals (CIs).
(2) Includes 86 participants (involving no new HCV infections) who were receiving opioid substitution treatment but reported no injections in the last month (cross-sectional studies) or last year (cohort studies).
Source: Turner et al. (2011).

prevalence of chronic HCV infection among people who inject drugs could have been as high as 70 %, rather than the 40 % seen today (Vickerman et al., 2012b) (Figure 4.1). However, further harm reduction scale-up may achieve only modest reductions in prevalence, over a very long time (20 years), and will necessitate levels of coverage that are unachievable or unsustainable (Vickerman et al., 2012a).

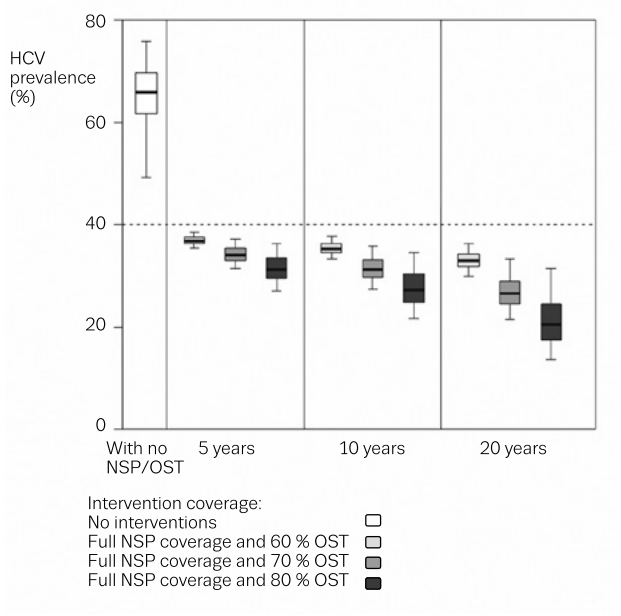
The prevalence of HCV infection among people who inject drugs varies considerably within and between European countries (Chapter 1) — but in most sites will be between 20 % and 60 %. In settings with low levels of harm reduction interventions, or none, scaling up opioid substitution treatment and high-coverage needle and syringe programmes can reduce the prevalence of chronic HCV infection among people who inject drugs by up to 40 % within 10 years, depending on the baseline level of chronic infection (Figure 4.2). However, despite the substantial potential impact of harm reduction on HCV transmission, model projections suggest that reducing the prevalence of HCV infection among people who inject drugs by more than 40 % within 10 years requires the introduction and scaling-up of hepatitis C treatment (Martin et al., 2013a) (Figure 4.2). Therefore, a combined strategy that includes hepatitis C treatment as a prevention measure is critical if HCV prevalence or transmission is to be reduced to very low levels, especially in settings where existing coverage of harm reduction interventions is high.

Potential impact of hepatitis C treatment for prevention among people who inject drugs

The dramatic improvements in hepatitis C treatment in recent years (see Chapter 5) has led to speculation about whether antiviral treatment could be used as an effective prevention strategy among people who inject

FIGURE 4.1

Modelling the projected impact of changes in the coverage of opioid substitution treatment and needle and syringe programmes in the United Kingdom (assuming a baseline prevalence of chronic HCV infection among people who inject drugs of 40 %) from 50 % for each intervention to 0, 60, 70 and 90 % for opioid substitution treatment and 100 % for needle and syringe programmes



NB: High-coverage needle and syringe programmes (100 % NSP) are those providing one or more sterile syringes for each injection reported per month. The box plots signify the uncertainty (middle line is median, limits of boxes are 25th and 75th percentiles and whiskers are 2.5th and 97.5th percentiles).
Source: Vickerman et al. (2012a).

drugs (Hellard et al., 2014). In theory, hepatitis C treatment could be even more effective a prevention measure than HIV treatment because hepatitis C treatment is finite and curative.

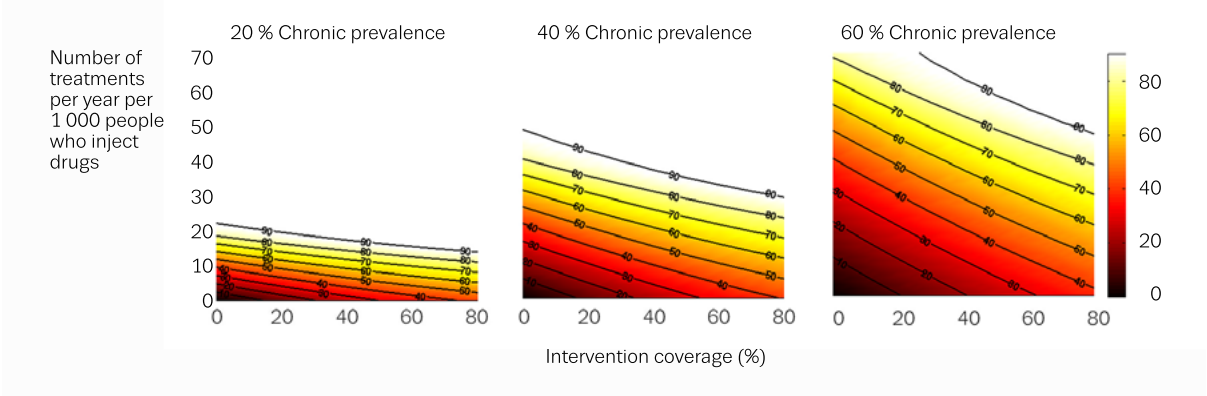
No empirical studies have explored whether hepatitis C treatment can reduce the prevalence of HCV infection among people who inject drugs and prevent onwards transmission. However, several theoretical modelling studies have indicated that comparatively modest rates of hepatitis C treatment in this group, using either interferon and ribavirin or direct-acting antiviral therapies, can result in dramatic reductions in HCV chronic prevalence within 10 to 15 years in a range of settings (Zeiler et al., 2010; Martin et al., 2011a,b,c, 2013a; Vickerman et al., 2011; Durier et al., 2012; Rolls et al., 2013; Cousien et al., 2016).

A recent evaluation of selected services in the United Kingdom found that treatment rates among people who inject drugs varied greatly (ranging from fewer than 5 to 27 per 1 000 injectors per year) (Martin et al., 2015b). Furthermore, model projections indicate that, in general, current hepatitis C treatment rates among people who inject drugs are insufficient to lead to an observable decline in the prevalence of HCV infection in the next decade (Martin et al., 2015b), as shown in Figure 4.3.

However, model projections have also shown that an achievable increase in hepatitis C treatment rates among people who inject drugs with direct-acting

FIGURE 4.2

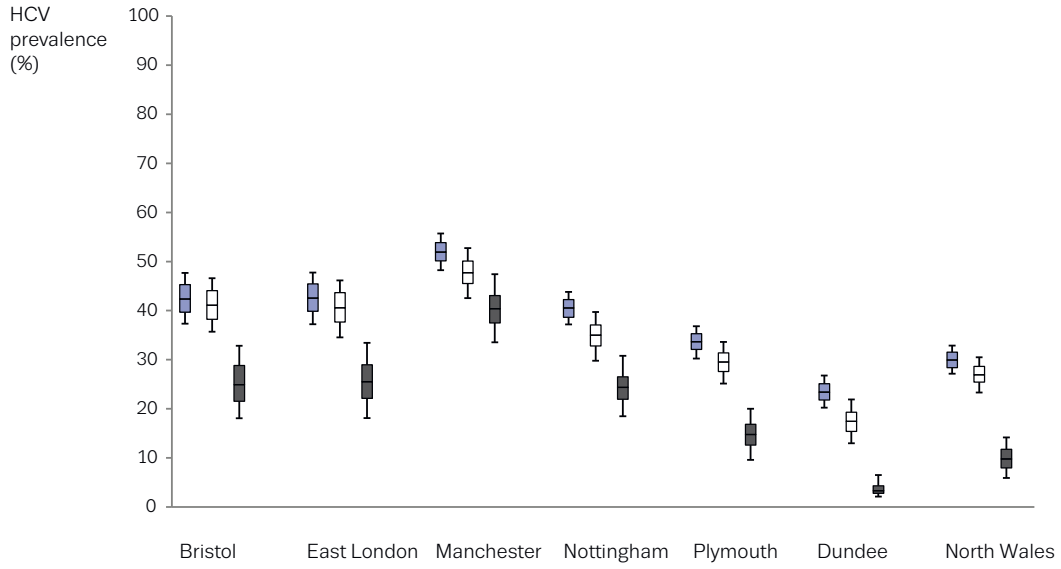
Modelling of the combined impact of hepatitis C antiviral treatment, opioid substitution treatment and high-coverage needle and syringe programmes on relative reduction of HCV chronic prevalence (%) over 10 years in a population of people who inject drugs when the baseline prevalence of chronic hepatitis C is 20 %, 40 % or 60 %



NB: The heat colours show the percent relative reduction in chronic HCV at 10 years, which ranges from 0 (dark brown) to over 80 % (white), achieved depending on the coverage of combined hepatitis C antiviral treatment among people who inject drugs (y-axis), opioid substitution treatment and high-coverage needle and syringe programmes (x-axis). Gradient lines show the contours of relative reductions in 10 % increments (e.g. 10 % relative reduction up to 90 % relative reduction).
Source: Martin et al. (2013a).

FIGURE 4.3

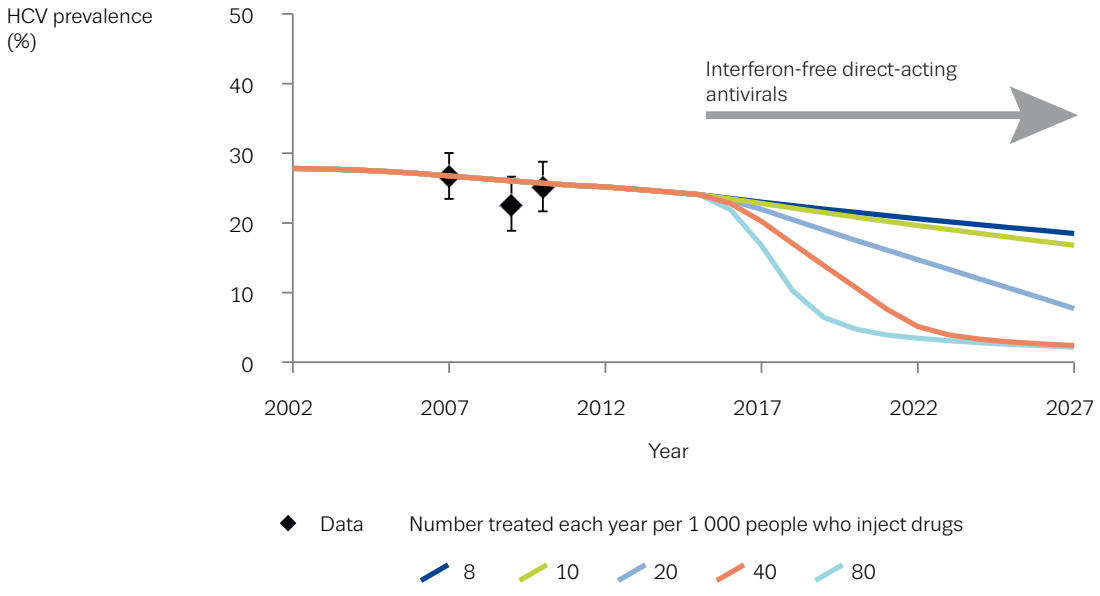
Box–whisker plot showing chronic HCV prevalence among people who inject drugs in 2014 (blue boxes) and projected HCV prevalence in 2024 with current (white boxes) and scaled-up (black boxes) hepatitis C treatment rates at multiple UK sites



NB: The blue boxes show estimated chronic HCV prevalence among people who inject drugs in 2014. The white boxes show the projected effects of no treatment scale-up of current HCV treatment rates, using pegylated interferon and ribavirin sustained viral response rates from 2005.The black boxes show the effect of scaling up treatment to the rate of 26/1000 people who inject drugs (as is currently achieved in Manchester), using interferon-free direct-acting antiviral medicines that can achieve 90 % sustained viral response rates for infection with all HCV genotypes in 2016.
Boxes show the interquartile range and whiskers the 95 % confidence intervals.
Source: Martin et al. (2015b).

FIGURE 4.4

Model projections of HCV chronic prevalence among people who inject drugs over time in Edinburgh, Scotland, assuming scale-up of hepatitis C treatment and interferon-free direct-acting antiviral therapy which achieve sustained virological response rates of 90 % from 2015



NB: Simulations show no scale-up from baseline (dark blue) or scaling up to the level of 10, 20, 40 or 80 per 1 000 people who inject drugs treated annually. The model assumes no treatment prior to 2002, linear scale-up to baseline treatment rates during 2002–07 and baseline treatment rates during 2007–15, then linear scale-up from baseline to the scaled-up rate during 2015–17. HCV prevalence data points with 95 % confidence intervals are shown for comparison.
Source: Martin et al. (2013b).

antiviral therapy with 90 % sustained viral response could lead to substantial reductions in the prevalence of HCV infection in the population (Figure 4.3). For example, in Edinburgh (Figure 4.4) a doubling of hepatitis C treatment rates could halve chronic HCV prevalence and incidence within 10 years (which corresponds to an increase from 32 to 64 drug injectors treated per year) (Martin et al., 2013b). If, at the same time, opioid substitution treatment and high-coverage needle and syringe programmes are also expanded, then either the impact will be greater or fewer expensive antiviral treatments will be required to reduce the prevalence of HCV infection (Martin et al., 2013a). Further service evaluations and model projections are required in other European settings to establish hepatitis C treatment rates among people who inject drugs and by how much treatment (and other interventions) needs to be scaled up to achieve observable reductions in the prevalence and incidence of HCV infection.

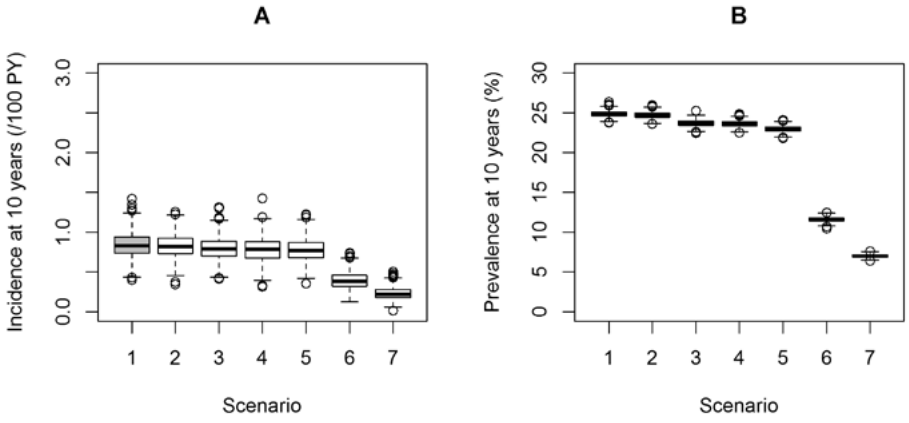
Two studies, one in Australia (Rolls et al., 2013) and one in France (Cousien et al., 2016), have modelled the impact of hepatitis C treatment for people who inject drugs using individual-based network models. Using detailed epidemiological data on the injecting network connections of people who inject drugs in Melbourne, Rolls et al. (2013) found that a strategy of treating all the contacts of an infected individual ('treat your friends') could be more effective than random treatment of people who inject drugs. Additionally, a recent modelling analysis in France (Figure 4.5) indicates that, because current hepatitis C treatment rates among people who inject drugs are relatively high, the introduction of direct-acting antiviral medicines that can achieve sustained virological response rates of 81 % could reduce the prevalence of chronic HCV infection among this group from 43 % at baseline to 25 % within 10 years (Cousien et al., 2016). However, current guidelines (European Association for the Study of the Liver, 2014) recommend that priority is given to those with moderate to severe liver disease (stages F2–F4), a strategy that is likely to have minimal impact on HCV transmission (scenarios 1 to 5 in Figure 4.5). Extending hepatitis C treatment to those earlier disease stages (F0/F1) — as shown by scenarios 6 and 7 — would have a dramatic impact on HCV incidence and prevalence due to a substantially increased pool of eligible people who inject drugs.

Cost-effectiveness of hepatitis C treatment for people who inject drugs

A number of studies have examined the cost-effectiveness of hepatitis C treatment for current or former drug injectors, consistently finding hepatitis C treatment for this risk group cost-effective (Table 4.2). The outcomes of these studies are incremental cost-effectiveness ratios (ICERs), which determine the incremental cost per health outcome gained (usually expressed in quality-adjusted life years, QALYs). These studies come from a variety of European and other developed countries (Australia, New Zealand, United

FIGURE 4.5

Modelling projections of the 10-year impact on HCV incidence (left) and prevalence (right) of hepatitis C treatment for people who inject drugs in France



NB: The model assumes a 10 % annual treatment delivery rate among eligible people who inject drugs. The scenarios are as follows: 1, current cascade of care (reference); 2, improvement in HCV testing; 3, improvement in linkage to care; 4, improvement in testing and linkage to care; 5, improvement in adherence to treatment; 6, treatment initiated at stage F0; 7, improvement of the entire cascade of care (combination of scenarios 4, 5 and 6).
Source: Cousien et al. (2016).

TABLE 4.2

Cost-effectiveness studies which have assessed hepatitis C treatment for people who inject drugs

Study	Country	Population	Intervention	Comparator	Reinfection	Includes prevention benefit	ICER (cost per QALY gained)
Leal et al. (1999)	United Kingdom	People who inject drugs in drugs services	Screening + interferon and ribavirin	No screening	No	No	GBP 9 300
Loubiere et al. (2003)	France	People who inject drugs	Screening + interferon and ribavirin	No screening	No	No	EUR 5 778
Sheerin et al. (2004)	New Zealand	People who inject drugs in substitution treatment	Substitution treatment + pegylated interferon and ribavirin	Only substitution treatment	No	No	NZD 19 000 (approx.) per life-year gained
Stein et al. (2004)	United Kingdom	People who inject drugs in drugs services	Screening + pegylated interferon and ribavirin	No screening	No	No	EUR 14 000 (approx.)
Thompson Coon et al. (2006)	United Kingdom	Former injectors in primary care	Case-finding + pegylated interferon and ribavirin	No case-finding	No	No	GBP 16 493
Wong et al. (2004)	United States	People who inject drugs	Interferon and ribavirin	No treatment	Yes (3–15 %/ year)	No	USD 5 600
Vickerman et al. (2008)	United Kingdom	People who inject drugs	Interferon and ribavirin	No treatment	Yes (*dynamic*)	Yes	GBP 10 500 (approx.)
Martin et al. (2012)	United Kingdom	Current and former drug injectors	Pegylated interferon and ribavirin	No treatment	Yes (*dynamic*)	Yes	Current injectors: GBP 500–8 000 (approx.) Former injectors: GBP 6 800 (approx.)
Visconti et al. (2013)	Australia	Current and former drug injectors	Pegylated interferon and ribavirin	No treatment	Yes (6.8 %/ year if injecting)	No	Current injectors: AUD 8 000 (approx.) Former injectors: AUD 6 000 (approx.)
Scott et al. (2016)	Australia	People who inject drugs	Early or late treatment with interferon-free direct acting antiviral therapy	No treatment	Yes (11 %/ year if injecting)	No	Late vs no treatment: AUD 5 078 Early vs late treatment: AUD 17 090
Martin et al. (2016b)	United Kingdom	Current and former drug injectors	Early treatment (mild or moderate fibrosis) with interferon-free direct acting antiviral therapy	Treatment at cirrhosis with interferon-free direct acting antiviral therapy	Yes (*dynamic*)	Yes	Mild/moderate injectors: GBP 2 800– 26 000 (approx.) depending on prevalence setting Mild former injectors: GBP 22 932 Moderate former injectors: GBP 13 081

NB: Costs are presented in original currency and price years. In 2016, EUR 1 = GBP 0.8 = USD 1.15 = AUD 1.5 = NZD 1.6.
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

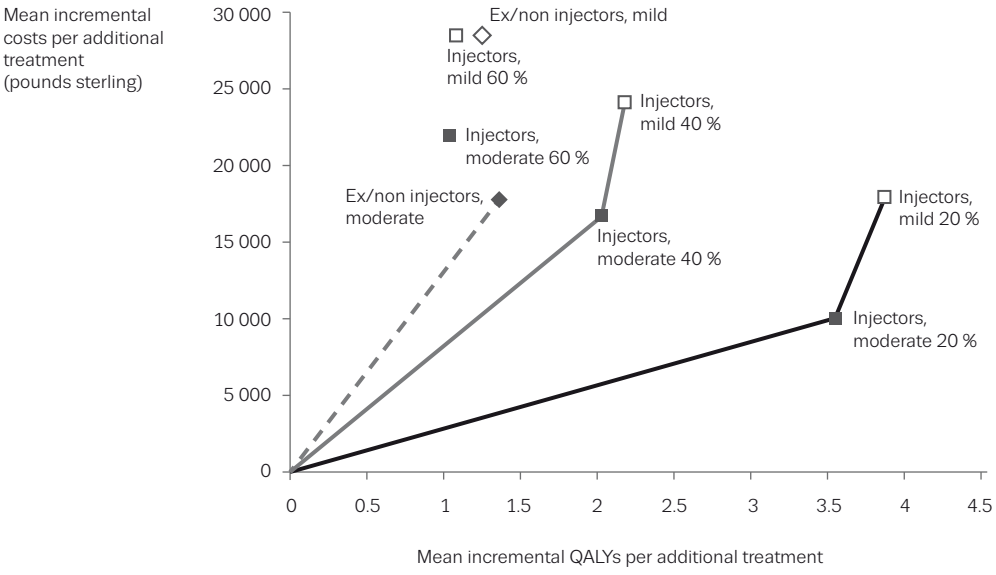
States) and make differing assumptions regarding the risk of reinfection. Only three studies include the possible prevention benefit of hepatitis C treatment (Vickerman et al., 2008; Martin et al., 2012, 2016b). Indeed, treating people who inject drugs may be more cost-effective than treating former or non-injectors because of the substantial benefits achieved through preventing secondary infections, despite the risk of reinfection or lower sustained virological response rates among injectors (Martin et al., 2012, 2016a).

The key questions, therefore, given a setting with limited resources, are which patients should be targeted as treatment is expanded, and which patients can wait. Considering that available resources are limited, current European guidelines recommend the prioritisation of direct-acting antiviral treatments for those with severe liver disease (European Association for the Study of the Liver, 2014). Updated guildelines in 2015 also recommend the prioritisation of those with on-going transmission risk, although it is unclear whether and to what degree this is being implemented across Eruope (European Association for the Study of the Liver, 2015). In Figure 4.6 we show the incremental costs and benefits of early treatment prioritisation based on liver disease stage (mild/moderate) and risk (injectors, former or non-injectors) compared with delaying treatment until compensated cirrhosis develops. The figure presents three population scenarios in which the prevalence of chronic hepatitis C among the drug-injecting population is 20 %, 40 % or 60 %. In populations with a very high prevalence of chronic hepatitis C (60 % or above), it is always more cost-effective to treat non-injectors with moderate disease, because of high levels of reinfection among people who inject drugs (Vickerman et al., 2016).

However, in settings in which the prevalence of chronic hepatitis C among people who inject drugs is 20 % or 40 %, the most cost-effective approach is to target those injecting drugs (with moderate and mild disease) *before* targeting non-injectors with moderate disease. Therefore, in settings in which the prevalence of chronic hepatitis C among people who inject drugs is below 60 %, both disease stage and risk factor information should be used to prioritise treatments. It is too early to make direct comparisons between specific interferon-free direct-acting antiviral medicines and current interferon-based regimens, as full cost-effectiveness studies, using dynamic models, of the new direct-acting antiviral medicines have not yet been undertaken — and the exact drug regime, the drug price and the population of patients recommended for treatment have not been established throughout Europe. However, we do know that hepatitis C treatment needs

FIGURE 4.6

Cost-effectiveness efficiency frontiers of early treatment for injectors or former injectors and non-injectors with mild or moderate hepatitis C using interferon-free direct-acting antiviral medicines, compared with delaying treatment until compensated cirrhosis develops, in the setting of a prevalence of chronic hepatitis C among people who inject drugs of 20 % (solid black line), 40 % (grey line) or 60 % (dashed grey line)



NB: The frontier curves show the most cost-effective option — HCV treatment for patient groups that do not lie on the frontier (and therefore lie above the lines shown) are dominated (are more expensive and provide fewer health benefits) by patient groups on the frontier.
Source: Martin et al. (2016a).

to be scaled up to make an appreciable impact on HCV transmission and that interferon-free direct-acting antiviral medicines will play role in enabling more patients to be treated and managed in the community. Undoubtedly direct-acting antiviral drug costs will need to be lower than suggested in some quarters (e.g. lower than GBP 35 000 for 12 weeks' treatment proposed in the *British National Formulary* (Joint Formulary Committee, 2014)) for the scale-up of hepatitis C treatment for prevention to be affordable by society.

Special populations: hepatitis C prevention in prison

Among the prison population both absolute numbers and the proportions of people who inject drugs are high and therefore, inevitably, rates of hepatitis C among prisoners are also high (Vescio et al., 2008). As a result, prison is an ideal setting for hepatitis C prevention interventions. In a recent study in Scotland, the risk of HCV transmission in prisons was found to be lower than that in the community, mainly because of widespread access to opioid substitution treatment in Scottish prisons (Hedrich et al., 2012; Taylor et al., 2013). However, studies carried out in prisons elsewhere in Europe have reported higher risk of blood-borne virus transmission in prison than the community (Stark et al., 1997; Christensen et al., 2000; Vescio et al., 2008; Arain et al., 2014). Prisons could play an important role in promoting public health and harm reduction among people who inject drugs. Rates of hepatitis B vaccination among people who inject drugs have increased as a result of prison programmes. Prisons also could have a role in hepatitis C case-finding and treatment — as people who inject drugs and who may not yet be in long-term opioid substitution treatment programmes, and, therefore, who are at continued risk of transmitting infection to others, can be detected and treated. A UK-based analysis showed that HCV testing in prisons, followed by 24–48 weeks' treatment with pegylated interferon and ribavirin in those testing positive, is cost-effective if continuity of care between prison and community can be achieved in at least 40 % of cases. In other words, because many people who inject drugs are incarcerated for relatively brief periods (on average 4 months in the United Kingdom), it is crucial to ensure that infected individuals are referred to treatment and remain in referral contact or on treatment after release or transfer. The high turnover of prisoners and frequent prison transfers in some countries therefore pose a challenge. Systems to ensure effective referral onto treatment and continuity of care are often not in place, which can substantially limit the effectiveness and cost-effectiveness of a prison-based treatment as a prevention strategy. Until now, the relatively long duration of hepatitis C treatment, problems of ensuring continuity of care in the community and short durations of imprisonment for drugs offences have militated against scaling up hepatitis C treatment in the prison setting. However, it is likely that treatments of shorter duration (8–12 weeks) will mean that a greater proportion of people who start on treatment while in prison will be able to complete it before being released, and this could make treatment in a prison setting more cost-effective (Martin et al., 2016b).

Importantly, a number of ethical issues regarding HCV testing and treatment in prison have been raised (Levy and Larney, 2015; Martin et al., 2015a). There is a need to ensure that HCV testing in prison is truly voluntary and not a result of coercion due to potentially unequal power relationships between prisoners and staff; and hepatitis C treatment should be offered alongside other harm reduction interventions (such as opioid substitution treatment) to reduce the risk of infection or reinfection.

Conclusions and implications

There is a strong theoretical basis for combining hepatitis C treatment with other primary prevention measures in order to reduce HCV transmission to negligible levels (so-called elimination). Although much of the modelling work has been done in a few countries, the scenarios reflect the situation in many European cities and, therefore, can be generalised. In most European cities and countries, after treating people with cirrhosis the next priority would be treating people who inject drugs — as greater benefit can be achieved by preventing secondary infections by treating people who inject drugs with mild and moderate disease than by delaying treatment until people develop cirrhosis or cease injecting. Furthermore, hepatitis C case-finding and treatment in prison could be a critical component of scaling up hepatitis C treatment in the community, although treatment in prison is likely to be cost-effective only with new oral direct-acting antiviral medicines and shorter (8–12 weeks) treatment durations. The model projections provide strong evidence for the hypothesis that hepatitis C treatment will reduce the prevalence of HCV infection and that treating people who inject drugs is cost-effective. Empirical data and evaluations of the impact of scaling up hepatitis C treatment among people who inject drugs in European settings are urgently needed.

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5

CHAPTER 5

Antiviral medications for hepatitis C virus infection

Jean-Michel Pawlotsky

Introduction

Traditional treatment of hepatitis C virus (HCV) with interferon and ribavirin could be effective, but these drugs were poorly tolerated and the duration of treatment was long (24–48 weeks). The definitive cure ([3]) of infection varied from under 20 % to 80 % in different patient groups and depending on HCV genotype (approximately 60 % overall). These factors have contributed to poor treatment uptake in the past decade. Now, however, the appearance on the market of new direct-acting antiviral drugs, which are effective against HCV, and the development of many others, is set to change the HCV treatment landscape in the coming years. The drugs currently available and those in development are reviewed in this chapter.

Available drugs

Pegylated interferon and ribavirin

For the past decade, HCV treatment has consisted of peginterferon and ribavirin. This treatment regimen was poorly tolerated and of long duration (24–48 weeks). Furthermore, sustained virological response rates were variable: approximately 45 % among those infected with HCV genotype 1, but 80 % in those with HCV genotype 2 or 3 infection; among older patients with more severe disease and unfavourable genotype, the rate was below 20 %. The burden of treatment was high: weekly interferon injections were accompanied by frequent surveillance and monitoring for potential side effects such as anaemia, depression and flu-like symptoms. These challenges have resulted in low treatment rates over the past decade, with treatment rates among those with chronic hepatitis C varying in most European countries between 1 % and 4 %; the highest rate was in France, at about 6 %.

Pegylated interferon-based treatments are now superseded in areas of the world that have access to oral-only interferon-free combinations, which are of shorter duration (8–24 weeks), highly tolerable and can achieve very high sustained virological response rates (> 90 %). Ribavirin remains a useful adjunct in some interferon-free treatment strategies, in which it is used to increase the sustained virological response rates, through mechanisms that are still to be elucidated.

Direct-acting antiviral drugs

Table 5.1 shows the direct-acting antiviral drugs that have been approved or are in clinical development at the time of writing (June 2016). Their antiviral effectiveness is high, but they differ in their activity against the different HCV genotypes (Smith et al., 2014) and in their barrier to resistance. Drugs are said to have a low barrier to resistance if their administration as a monotherapy rapidly selects fit resistant viral variants (Pawlotsky, 2011). Such resistant variants are naturally present in infected individuals, generally but not always as minor undetectable populations, and can multiply rapidly, i.e. become selected, with the result that the drug quickly becomes ineffective. Drugs with a high barrier to resistance do not result in the selection of such variants, either because these variants do not naturally pre-exist in infected patients (a high genetic barrier) or because they are not fit enough to replicate at clinically meaningful levels if selected (Pawlotsky, 2011). Combining drugs from different classes is mandatory to raise the barrier to resistance of the combination regimen.

([3]) Definitive cure of infection is defined as the achievement of a sustained virological response (SVR), in which HCV RNA is undetectable in blood 12 weeks (SVR12) or 24 weeks (SVR24) after the end of therapy.

TABLE 5.1
Direct-acting antiviral drugs approved or in clinical development

Class	Generation/wave		Compound	Manufacturer	Current status or phase of clinical development (published or presented)
Nucleotide analogues	1st-generation		Sofosbuvir	Gilead	Approved
			MK-3682	Merck	Phase II
			AL-335	Janssen	Phase II
NS5A inhibitors	1st-generation	1st-wave	Daclatasvir	Bristol-Myers Squibb	Approved
			Ledipasvir	Gilead	Approved
			Ombitasvir	Abbvie	Approved
		2nd-wave	Elbasvir	Merck	Approved (US, EU in 2016)
			Velpatasvir	Gilead	Approved
			Odalasvir	Janssen	Phase II
			Ravidasvir	Presidio	Phase II
	2nd-generation		Pibrentasvir	Abbvie	Phase III
			MK-8408	Merck	Phase II
NS3-4A protease inhibitors	1st-generation	1st-wave	Telaprevir	Janssen, Mitsubishi	Approved
			Boceprevir	Merck	Approved
		2nd-wave	Simeprevir	Janssen	Approved
			Paritaprevir/r	Abbvie	Approved
			Asunaprevir	Bristol-Myers Squibb	Approved (Asia, Middle East)
			Vaniprevir	Merck	Approved (Japan)
	2nd-generation		Grazoprevir	Merck	Approved (US, EU in 2016)
			Glecaprevir	Abbvie	Phase III
			Voxilaprevir	Gilead	Phase III
Non-nucleoside inhibitors of HCV RdRp	Palm-1 inhibitors		Dasabuvir	Abbvie	Approved

NB: ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir, grazoprevir/elbasvir, velpatasvir/sofosbuvir, glecaprevir/pibrentasvir and possibly other compounds are or will be available as single-pill, fixed dose combinations; /r, ritonavir-boosted.

NS3-4A protease inhibitors

NS3-4A protease inhibitors are peptidomimetic compounds that bind to the catalytic site of the enzyme NS3-4A protease and block post-translational processing of the viral polyprotein, preventing the release of functional non-structural proteins.

Two first-wave, first-generation NS3-4A protease inhibitors, telaprevir (Vertex, Janssen and Mitsubishi) and boceprevir (Merck) (Table 5.1), were approved in 2011 for use in combination with peginterferon and ribavirin in patients infected with HCV genotype 1 (Bacon et al., 2011; Jacobson et al., 2011; Poordad et al., 2011; Zeuzem et al., 2011). They are active against genotype 1 (telaprevir is also active against genotype 2) and have a low barrier to resistance. These combinations are no longer used because of their poor tolerance.

Second-wave, first-generation NS3-4A protease inhibitors are administered once or twice per day. They are active against genotypes 1, 2 and 4 at least, but not against genotype 3. They have a low barrier to resistance, and cross-resistance among drugs in this group and with telaprevir and boceprevir is extensive. Simeprevir (Janssen) (Rosenquis et al., 2014) was approved in November 2013 in the United States and in May 2014 in the European Union for use in patients infected with HCV genotype 1. It is also active against HCV genotype 4. Asunaprevir (Bristol-Myers Squibb) (McPhee et al., 2012) was approved for use in combination with the NS5A inhibitor daclatasvir in July 2014 for patients infected with HCV genotype 1b in several Asian countries. Paritaprevir (Abbvie) is boosted by ritonavir (100 mg/day) to extend dosing intervals while increasing patient exposure and reducing side effects; it was approved in 2015 in combination with the NS5A inhibitor ombitasvir in one single tablet, plus the non-nucleoside inhibitor of the RNA-dependent RNA polymerase (RdRp) dasabuvir as a different tablet (Table 5.1).

Second-generation NS3-4A protease inhibitors are purported to have pangenotypic antiviral activity. They have a higher barrier to resistance than first-generation drugs (Huang et al., 2010; Lahser et al., 2012), but they select resistant variants that are selected by first-generation compounds (Huang et al., 2010; Lahser et al., 2012). They include grazoprevir (Merck) (Summa et al., 2012), which will be available in combination with the NS5A inhibitor elbasvir in one single tablet in 2016, as well as voxilaprevir or GS-9857 (Gilead) and glecaprevir or ABT-493 (Abbvie), currently in Phase III clinical development (Table 5.1).

Nucleotide analogue inhibitors

Nucleotide analogues act as false substrates for the HCV RNA-dependent RNA polymerase (RdRp). They lead to chain termination after being incorporated into the newly synthesised viral RNA. Activation of nucleotide analogues requires two phosphorylations. Owing to their mechanism of action, nucleotide analogues are active against all HCV genotypes. They have a high barrier to resistance, because the viral variants they select do not replicate at high levels. The nucleotide analogue sofosbuvir (Gilead) (Sofia et al., 2010) was approved in the United States in December 2013 and in the European Union in January 2014. Other nucleotide analogues in clinical development include MK-3682 (Merck) and AL-335 (Janssen) (Table 5.1).

Non-nucleoside inhibitors of the HCV RNA-dependent RNA polymerase

Non-nucleoside inhibitors of HCV RdRp bind to one allosteric site at the surface of the enzyme (Haudecoeur et al., 2013). By altering the conformation of the RdRp, they block its catalytic function, thereby indirectly blocking RNA replication. Non-nucleoside HCV RdRp inhibitors are generally active mainly against HCV genotype 1 and have a low barrier to resistance. HCV RdRp is known to have a right-hand shape, with a thumb, a palm and finger domains. The palm I domain inhibitor dasabuvir has been approved in 2015 for use in combination with the ritonavir-boosted NS3-4A protease inhibitor paritaprevir and the NS5A inhibitor ombitasvir (Table 5.1).

NS5A inhibitors

NS5A inhibitors bind to domain 1 of the NS5A protein and block its ability to regulate HCV replication within the replication complex (Pawlotsky, 2013). In addition, NS5A inhibitors inhibit assembly and release of viral particles (Guedj et al., 2013; McGivern et al., 2014). This dual mechanism explains the potent and rapid shutdown of virus production during the first days of their administration. First-generation NS5A inhibitors have pangenotypic activity, except ledipasvir which has limited activity against genotypes 2 and 3. They have a low barrier to resistance (Pawlotsky, 2013). Daclatasvir (Bristol-Myers Squibb) (Gao et al., 2010) was approved in the European Union in September 2014 and in the United States in 2015. It has been used in combination with sofosbuvir in many European early access programmes for different genotypes and this combination currently is the standard-of-care for

patients with HCV genotype 3 infection. Ledipasvir (Gilead) (Link et al., 2014) was approved at the end of 2014 as a single tablet regimen in combination with sofosbuvir for genotypes 1, 4, 5 and 6, while ombitasvir (Abbvie) (Degoey et al., 2014) was approved within the same timeframe for use in combination with ritonavir-boosted paritaprevir (one single tablet) with or without dasabuvir for genotypes 1 and 4, respectively (Table 5.1).

Second-wave, second-generation NS5A inhibitors have pangenotypic activity. Their barrier to resistance is slightly higher than that of first-generation NS5A inhibitors (Lahser et al., 2012), but they select resistant viruses that are also selected by first-generation compounds. They include elbasvir (Merck), which will be available in combination with grazoprevir in one single tablet (Coburn et al., 2013), velpatasvir (Gilead), which will be available in combination with sofosbuvir in one single tablet, odalasvir (Janssen) and ravidasvir (Presidio) (Yang et al., 2012).

Second-generation NS5A inhibitors should have a substantially improved barrier to resistance compared to first-generation drugs. They include pibrentasvir or ABT-530 (Abbvie), which will be available in combination with glecaprevir in one single tablet, and MK-8408 (Merck) (Table 5.1).

Current HCV treatment regimens (2016)

Three new direct-acting antiviral drugs for the treatment of HCV infection were approved as single agents in 2014 and 2015 in the United States and Europe, sofosbuvir, simeprevir and daclatasvir. The fixed-dose combination of sofosbuvir and ledipasvir in one single pill was approved in early 2015, as well as the combination of ritonavir-boosted paritaprevir and ombitasvir in one single pill with or without dasabuvir according to the genotype. The combination of grazoprevir and elbasvir was approved in late 2015 in the United States and will be approved in mid-2016 in Europe, the combination of sofosbuvir and velpatasvir was approved in 2016 on both continents. This offers a number of options for interferon-free combination therapy. Interferon-free options include: sofosbuvir plus ribavirin (genotype 2); sofosbuvir plus simeprevir, with or without ribavirin (genotypes 1 and 4); sofosbuvir plus daclatasvir, with or without ribavirin (all genotypes); sofosbuvir-ledipasvir, with or without ribavirin (genotypes 1, 4, 5 and 6); ritonavir-boosted paritaprevir and ombitasvir plus dasabuvir, with or without ribavirin (genotype 1); ritonavir-boosted paritaprevir and ombitasvir, with ribavirin (genotype 4); grazoprevir-elbasvir, with or without ribavirin (genotypes 1 and 4). Sofosbuvir-velpatasvir, with or without ribavirin (all genotypes). Peginterferon and ribavirin-based regimens should be used only when interferon-free regimens are not available.

Sofosbuvir plus ribavirin

This combination is indicated in patients infected with HCV genotypes 2 and 3. However, it is suboptimal in genotype 3 and other options should be preferred. In FISSION (Lawitz et al., 2013b), sofosbuvir plus ribavirin treatment for 12 weeks in treatment-naive patients yielded sustained virological response rates of 95 % in patients infected with HCV genotype 2 (Lawitz et al., 2013b). In POSITRON, 93 % of patients with genotype 2 infection who were ineligible for or intolerant to interferon-based therapy achieved a sustained virological response after 12 weeks of therapy (Jacobson et al., 2013b). In FUSION, the sustained virological response rate after 12 or 16 weeks of treatment was 82 % and 89 %, respectively, among patients infected with HCV genotype 2 (Jacobson et al., 2013b). Finally, in the VALENCE trial, participants infected with HCV genotype 2 were treated with combined sofosbuvir plus ribavirin for 12 weeks. The sustained virological response rate was 97 % in treatment-naive patients without cirrhosis, 100 % in treatment-naive patients with cirrhosis, 91 % in treatment-experienced patients without cirrhosis and 88 % in treatment-experienced patients with cirrhosis (Zeuzem et al., 2014a). The combination of sofosbuvir and ribavirin was well tolerated.

Sofosbuvir plus simeprevir

In the phase II COSMOS trial of sofosbuvir plus simeprevir, the first cohort of participants comprised patients with mild to moderate fibrosis (grades 0–2) according to the METAVIR system, who had previously failed to respond to treatment. Among this group, the sustained virological response rate after 24 weeks was 79 % among those who did not receive concomitant ribavirin and 93 % among those who did. The corresponding rates after 12 weeks' treatment were 96 % and 93 %. In the second cohort, comprising patients with more severe fibrosis (grade 3 or 4), the sustained virological response rate at week 4 was 100 % among treatment-naive patients, with or without concomitant ribavirin; among those who had previously failed to respond to treatment the sustained virological response was 100 % in those also receiving ribavirin and

93 % in those who did not receive it (Jacobson et al., 2013c). Three patients who failed to achieve a sustained virological response were infected with HCV genotype 1a and had a detectable Q80K substitution in the NS3 protease sequence at baseline; however, infection was eliminated in the majority of such patients with this regimen. The combination was well tolerated (Jacobson et al., 2013c). These results were confirmed in two Phase III studies in patients with genotype 1. In OPTIMIST-1, in non-cirrhotic patients 12 weeks of sofosbuvir and simeprevir yielded sustained virological response rates of 97 % and 95 % in treatment-naive and treatment experienced patients, respectively (Kwo et al., 2016) In OPTIMIST-2, in treatment-naive patients with cirrhosis, the rate of cure of infection with sofosbuvir and simeprevir was 88 % overall, 84 % in patients with genotype 1b infection, 92 % in those with genotype 1a without Q80K, and 74 % in those with genotype 1a with Q80K (Lawitz et al., 2016). Recent real-world data indicate that the combination of sofosbuvir and simeprevir is less efficacious than other sofosbuvir-based combinations.

Sofosbuvir plus daclatasvir

Sulkowski et al. (2014) assessed 24 weeks' treatment with a combination of sofosbuvir and daclatasvir, with or without ribavirin, in treatment-naive patients and patients who had previously failed to respond to a combination of pegylated interferon, ribavirin and either telaprevir or boceprevir. In the treatment-naive group, the sustained virological response rate among those infected with HCV genotype 1 was 100 % with or without ribavirin and among those infected with genotypes 2 or 3 was 100 % with ribavirin and 93 % without ribavirin. The corresponding rates in the group of previous non-responders were 100 % and 95 %, respectively. Forty of the 41 treatment-naive patients infected with HCV genotype 1 treated with sofosbuvir and daclatasvir without ribavirin had achieved an SVR by 12 weeks (the remaining patient was lost to follow-up) (Sulkowski et al., 2014). This drug combination was well tolerated. The efficacy of this regimen has been confirmed in patients with genotype 1 with various severities of liver disease, including in decompensated cirrhosis and in the post-transplant setting, both in clinical trials and in real-world studies.

The use of sofosbuvir and daclatasvir as first-line treatment for patients infected with genotype 3 is supported by two Phase III studies. In ALLY-3, with sofosbuvir and daclatasvir, 12 weeks in non-cirrhotic patients, the rates of sustained virological response were 97 % and 94 % in treatment-naive and treatment-experienced patients, respectively (Nelson et al., 2015). In ALLY-3+, 83 % and 89 % of cirrhotic patients responded to 12 and 16 weeks of sofosbuvir and daclatasvir with ribavirin, respectively. No data is available with 24 weeks with this regimen (Leroy et al., 2016).

Sofosbuvir plus ledipasvir

The results of three phase III trials of treatment-naive and treatment-experienced patients infected with HCV genotype 1 who received the combination of sofosbuvir

TABLE 5.2

Rates of sustained virological response at 12 weeks (SVR12) in the ION-1, ION-2 and ION-3 phase III trials in patients infected with HCV genotype 1 treated for 8–12 weeks with a fixed-dose combination of sofosbuvir and ledipasvir, with or without ribavirin (Afdhal et al., 2014a,b; Kowdley et al., 2014)

Phase III trial	Patient population	Treatment duration (weeks)	Ribavirin	SVR12
ION-1	Treatment naive	12	No	98 % (209/214)
			Yes	97 % (211/217)
		24	No	98 % (213/217)
			Yes	99 % (215/217)
ION-3	Treatment naive	8	No	94 % (202/215)
			Yes	93 % (201/216)
		12	No	95 % (206/216)
ION-2	Treatment experienced	12	No	94 % (102/109)
			Yes	96 % (107/111)
		24	No	99 % (108/109)
			Yes	99 % (110/111)

NB: Proportion of participants with cirrhosis: ION-1, 16 %; ION-2, 20 %; ION-3, 0 %.

and ledipasvir in a fixed-dose combination (i.e. a single pill containing both drugs) were reported (Table 5.2) (Afdhal et al., 2014a,b; Kowdley et al., 2014).

In ION-1, in treatment-naive patients, the sustained virological response rate after 12 weeks of treatment was 98 % and 97 % with or without ribavirin, respectively, and 99 % and 98 %, respectively, after 24 weeks of treatment (Afdhal et al., 2014a).

In ION-3, in treatment-naive patients with mild to moderate liver disease (fibrosis grade 0–2), the sustained virological response rate among those receiving 8 weeks' treatment was 94 % without ribavirin and 93 % with ribavirin; among those treated for 12 weeks with combined sofosbuvir plus ledipasvir but without ribavirin the sustained virological response was 95 % (Kowdley et al., 2014).

In ION-2, treatment-experienced patients were treated for 12 or 24 weeks with sofosbuvir plus ledipasvir with or without ribavirin. After 12 weeks of therapy, the sustained virological response rate was 94 % with and 96 % without ribavirin. After 24 weeks of therapy, the corresponding rates were 99 % and 99 %, respectively (Afdhal et al., 2014b). No major safety signal was reported.

With 12 weeks of sofosbuvir and ledipasvir with ribavirin, high rates of sustained virological response (85–90 %) were also reported in patients with Child-Pugh B or C decompensated cirrhosis, and in patients with an HCV recurrence after liver transplantation (96 % in patients without cirrhosis and in those with compensated liver disease, 85 % in those with Child-Pugh B and 60 % in those with Child-Pugh C decompensated cirrhosis) (Charlton et al., 2015).

The safety and efficacy of the sofosbuvir–ledipasvir combination was confirmed in a large number of large-scale real-world studies.

Ritonavir-boosted paritaprevir and ombitasvir plus dasabuvir

The results of six phase III clinical trials of ritonavir-boosted paritaprevir co-formulated with ombitasvir and dasabuvir have recently been reported. Patients with HCV genotype 1 infection, with and without cirrhosis, received the combination with or without ribavirin for 12 or 24 weeks. The results are summarised in Table 5.3.

In SAPPHIRE-I, treatment-naive patients without cirrhosis were treated for 12 weeks with the combination plus ribavirin. The sustained virological response rate was 95 % in those infected with subtype 1a and 98 % in those infected with subtype 1b (Feld et al., 2014).

In PEARL-IV, participants infected with HCV subtype 1a were treated with combined ritonavir-boosted paritaprevir plus ombitasvir plus dasabuvir with or

TABLE 5.3

Rates of sustained virological response at 12 weeks (SVR12) in the SAPPHIRE-I, SAPPHIRE-II, PEARL-II, PEARL-III, PEARL-IV and TURQUOISE-II phase III trials in patients infected with HCV genotype 1 treated for 12 or 24 weeks with ritonavir-boosted paritaprevir co-formulated with ombitasvir and dasabuvir with or without weight-based ribavirin (Feld et al., 2014; Ferenci et al., 2014; Poordad et al., 2014; Zeuzem et al., 2014b)

Phase III trial	Patient population		Treatment duration (weeks)	HCV subtype	Ribavirin	SVR12
	Previous treatment	Cirrhosis				
SAPPHIRE-I	Treatment naive	No	12	1a	Yes	95 % (307/322)
				1b	Yes	98 % (148/151)
PEARL-IV	Treatment naive	No	12	1a	No	90 % (185/205)
					Yes	97 % (97/100)
PEARL-III	Treatment naive	No	12	1b	No	99 % (209/210)
					Yes	99 % (207/209)
SAPPHIRE-II	Treatment experienced	No	12	1a	Yes	96 % (166/173)
				1b	Yes	97 % (119/123)
PEARL-II	Treatment experienced	No	12	1b	No	100 % (91/91)
					Yes	97 % (85/88)
TURQUOISE-II	Mixed	Yes	12	Mixed	Yes	92 % (191/208)
			24		Yes	96 % (165/172)

without ribavirin. The sustained virological response rate was 97 % and 90 %, respectively. Participants in PEARL-III were infected with HCV subtype 1b and received the same drug combination, again with or without ribavirin. The sustained virological response rate was 99 % in both groups (Ferenci et al., 2014).

In SAPPHIRE-II, treatment-experienced patients without cirrhosis were treated with ritonavir-boosted paritaprevir plus ombitasvir plus dasabuvir for 12 weeks. The sustained virological response rate was 96 % among those infected with subtype 1a and 97 % in the group infected with subtype 1b.

In PEARL-II, in which treatment-experienced participants were infected with HCV subtype 1b, the sustained virological response rate was 97 % among those treated with the combination plus ribavirin and 100 % in the group that did not receive ribavirin (Zeuzem et al., 2014b).

In TURQUOISE-II, participants were treatment-naive and -experienced patients with HCV genotype 1 infection and compensated cirrhosis. The sustained virological response rate was 92 % after 12 weeks and 96 % after 24 weeks (Poordad et al., 2014). Sustained virological response rates among patients with cirrhosis and those who had previously not responded to interferon-based therapy were higher at 24 weeks than at 12 weeks. A more recent study, TURQUOISE-III, has shown that ribavirin is not needed in combination with this regimen administered 12 weeks in patients with cirrhosis and genotype 1b infection (Feld et al., 2016).

In all studies, this drug combination was well tolerated. The safety and efficacy of this combination has now been confirmed in a large number of large-scale real-world studies.

Future HCV treatment regimens

Future treatment regimens will include second-generation drugs belonging to the same classes, i.e. drugs with improved intrinsic performance, in particular a higher barrier to resistance, and/or triple combination of drugs from different classes. The combinations of grazoprevir and elbasvir and of sofosbuvir and velpatasvir will be available in the European Union by the end of 2016. Looking further ahead, regimens in advanced stages of development include the combination of glecaprevir and pibrentasvir in one single tablet and the combination of sofosbuvir, velpatasvir and voxilaprevir, currently in Phase III clinical evaluation.

Conclusion

The treatment of HCV infection has changed dramatically from 2014–2015. All-oral, interferon-free regimens now prevail. Global control of infection has been set as a reasonable objective for 2020–2030 by many countries. As the number of options increases, it can only be hoped that drug prices will decrease and that access to therapy will be provided to all those in need.

Conflict of interest disclosure

The author has received research grants from Gilead Sciences. He has served as an advisor for Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen and Merck.

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6

CHAPTER 6

Scaling up hepatitis C treatment: taking into account the needs and perspectives of people who inject drugs

Magdalena Harris and Tim Rhodes

Introduction

The landscape of hepatitis C (HCV) treatment is changing. The promise of interferon-sparing or interferon-free regimes, accompanied by moves to integrate HCV treatment into community settings and clinical guidance promoting relaxed eligibility criteria (Alavi et al., 2013; EASL, 2014), holds the potential to break down current barriers to HCV treatment access and uptake for people who inject drugs. Research exploring the HCV treatment perspectives of people who inject drugs has found that concerns about side effects, limited knowledge of HCV, worries that treatment will be rationed, experiences of treatment refusal owing to drug use, competing priorities, stigma, criminalisation and difficult-to-access services pose significant hurdles to HCV treatment contemplation, access and uptake (Doab et al., 2005; Grebely et al., 2008; Harris and Rhodes 2013; Rhodes et al., 2013; Swan et al., 2010; Treloar et al., 2013; WHO Regional Office for Europe, 2012). While changes in the HCV treatment landscape can have a positive impact on some of these issues, there is a need for a concomitant enabling environment interventions informed by the needs and perspectives of people who inject drugs. In this chapter, we draw on recent qualitative research carried out at the London School of Tropical Medicine and Hygiene (see box) among people who inject drugs to illustrate three components of enabling interventions and their role in facilitating HCV treatment engagement, initiation and access.

We consider three key themes or enabling environments in order to address health inequities and inequalities in HCV treatment access and to promote and increase uptake of HCV treatment among people who inject drugs.

Enabling living environments: facilitating engagement

For many people who inject drugs HCV is seen as a long-term concern, something that may be viewed as of lower priority than more immediate short-term issues, such as acute health problems, homelessness, incarceration and poverty (Harris and Rhodes, 2013; Rhodes and Treloar, 2008). Services that have the capacity to address these immediate concerns can provide a space for HCV treatment contemplation. Here we consider the example of accommodation. Rufus and George, both long-term homeless, spoke of the role of individual providers as 'access points' in helping them to secure housing. Having a stable place to live was experienced as transformative, facilitating a change in priorities and leading to HCV treatment contemplation and commencement. As Rufus says:

> *It's just the feeling of security, I've never had that feeling of security... It changes everything absolutely, it gives you a base you can build on... it gives me the ability to think long term as well which is things like coming for treatment, sorting my treatment out, sorting out my methadone treatment and sorting out my hepatitis C treatment... [having a flat] made me feel a lot better about everything.*

While some community-based services in the United Kingdom will facilitate HCV treatment for people who are homeless, study participants rarely felt that this was the right time for them. As George says:

> *Then I got the flat... I'm settled now, we talked about it [HCV treatment] while I was on the streets but I didn't want to do it then, I didn't think it would be the right way to go about it, being on the streets and all that.*

Being made homeless can also undo HCV treatment possibility. When Alec was first interviewed, he was preparing to start HCV treatment. At the second interview, some 6 months later, he was yet to start — speaking of the havoc wrought in his life by losing his accommodation:

> *I was made street homeless in July … I had to go to hospital. I had twenty admissions for being drunk and I got really ill … I had to drink just to cope with my situation, it was really bad.*

Although the advent of interferon-sparing or interferon-free regimes with a favourable side-effect profile might increase treatment possibility for people who are homeless, the contingencies of managing life on the streets means that HCV treatment is unlikely to be of high priority.

Access to low-threshold opioid substitution treatment — as with the provision of stable accommodation — can facilitate HCV contemplation and completion. The mechanisms of opioid substitution treatment provision are important in this regard, with takeaway dose provision facilitating expressions of trust, self-worth and treatment engagement (Harris et al., 2013). As Jeff says:

> *I get it [methadone] weekly, I've been trusted for a long time… The hepatitis [treatment], the last thing you want is to run out to the chemist and get your medicine and come back… it is a great help having it there.*

Conversely, Hakki — on supervised consumption — feels untrusted/unworthy and is loath to engage:

> *I've been on the [methadone] script for about 8 months now and they still supervise. I don't know what they think I'm going to do… I'm too angry with the system at the moment. I don't really engage… why don't they trust me?*

Enabling treatment environments: facilitating initiation

Enabling living environments can assist HCV treatment contemplation; yet this is unlikely to translate into uptake and completion if treatment systems are difficult to access and engage with. Traditional hospital-based treatment poses a number of barriers to access and uptake, with high attrition rates between referral and specialist appointment documented among people who inject drugs (Knight, 2013). Reasons for people who inject drugs becoming disillusioned with or giving up on HCV treatment include the lengthy period between referral and first specialist appointment; multiple hospital appointment requirements to assess treatment 'readiness'; being refused treatment because of substance use; stressful and discriminatory encounters with service providers; missing postal reminders as a consequence of housing instability; missing rigid appointment slots because of life contingencies; and being discharged from the system as a result of 'do not attend' policies (WHO Regional Office for Europe, 2012; Rhodes et al., 2013).

Community-based treatment, such as that based in drug and alcohol settings, is well placed to overcome some of these barriers to access. This is particularly the case if

Qualitative studies on hepatitis C treatment

This paper draws on qualitative data from two studies carried out at the London School of Hygiene and Tropical Medicine.

The 'Hepatitis C treatment journey study' (2012–2016) is a qualitative longitudinal prospective study exploring the HCV treatment journey and needed supports from patient, provider and system perspectives. Data collection was primarily carried out at two London HCV treatment hospitals and one drug treatment service and comprised 100 hours of nurse-led HCV clinic observations and 92 in-depth interviews with 28 people living with HCV, 10 treatment providers and 8 stakeholders. The study is funded by the National Institute for Health Research (NIHR-PDF-2011-04-031).

The 'Barriers and facilitators to hepatitis C treatment for people who inject drugs: a qualitative study' (2011) explored the individual, social and structural factors shaping the accessibility and quality of HCV service delivery to people who inject drugs. Data collection was carried out at two London drug treatment services and comprised in-depth interviews with 35 people living with hepatitis C and 14 service providers. The study was funded by the European Commission Directorate of Health and Consumers, the World Health Organization Regional Office for Europe and the National Institute for Health Research.

trusting relationships are able to be facilitated with providers and holistic care is offered in a 'one-stop-shop' format (Birkhead et al., 2007; Harris et al., 2013; WHO Regional Office for Europe, 2012). Continuity of care was considered to be important, with some participants expressing frustration at high staff turnover and the difficulty of fully engaging in such circumstances:

> *I didn't feel that where I was with this key worker, I wasn't 100 % secure with him... I just didn't have a real connection with anyone up there ... I think it's pretty invasive sort of treatment, you go through quite a lot of crap ... it helps a lot to be able to talk to someone properly. (Davey)*

Although people who inject drugs might have an ambivalent relationship with drug and alcohol services, their familiarity and convenience can encourage treatment engagement. As Davey also says, 'it [D&A service] was a familiar place to us and that's what made us think, I'll come back and I'll try it [HCV treatment]'. Jeff speaks of the convenience of seeing two providers under the same roof:

> *When I came in [it is] like killing two birds with one stone. When I came in on my fortnight thingy, I'd see my key worker [and] I'd always see [HCV nurse]. So I'd deal with that and then I'd deal with that at the same time.*

Drug and alcohol services are often more amenable to modification than hospitals, particularly in regard to the creation of responsive, flexible treatment systems. Appointment and phlebotomy systems are two examples. Flexible appointment systems, comprising open slots and no do not attend policy, allow for the contingencies of people who inject drugs' daily lives and encourage access. James explains:

> *[Flexibility is important] because sometimes you don't know how you are going to be feeling... you get your ups and your downs, it's a tackle each day really. You've got bad drug habits, drink habits, depression.*

Many people who inject drugs have difficult venous access and can find phlebotomy procedures stressful and stigmatising. This is particularly the case in environments where phlebotomists are restricted to the venous sites they can access, and are reluctant to acknowledge the expertise of people who inject drugs in this process. As Dillon relates:

> *I kept on saying to [hospital phlebotomist], 'Look, you know, my veins are a nightmare, you know, let me do it'. [She said] 'Oh you people, you think you know about your veins and all that, when you know nothing'.*

Such experiences can act to perpetuate mistrust and facilitate disengagement. The provision of on-site phlebotomy service, where blood is taken as part of a collaborative process, with protocols in place for jugular, femoral and client self-access, can assist the development of trusting relationships and HCV treatment engagement (Alavi et al., 2013).

Enabling policy environments: facilitating access

Clinical guidelines at a UK and European level recommend that current injecting by itself is not a contraindication to HCV treatment access (NICE, 2004; EASL, 2014). Yet, in the United Kingdom, where these guidelines have been in place since 2004, eligibility criteria are unevenly deployed. A 2010 UK audit of hospitals delivering HCV services found that one in seven hospitals refuses NICE-approved treatment to all people who inject drugs (All-Party Parliamentary Hepatology Group, 2010). As Shane reports:

> *I think their exact words were 'it's an expensive drug, you're using on top and we're not treating people who are using, because you could get re-infected couldn't you?'*

Experiences of, and circulation of narratives about, treatment refusal contribute to institutional mistrust and diminished treatment expectation among people who inject drugs. Although current innovations in HCV treatments bring to mind early developments in the treatment of human immunodeficiency virus (HIV), related activism and expectation among the primary affected communities differs considerably — reflected in the comment below:

> *They [people who inject drugs] have such low self-esteem, they won't make a fuss, and they really don't jump up and down. The idea that tranches of people with haemophilia could not be offered hepatitis C treatment because it was inconvenient or something, it's just an extraordinary concept and they would make a huge fuss, but the drug users just accept that they're not worth it and they won't go there. (Hepatology consultant)*

A feeling of being undeserving of treatment is unsurprising given the circumstances of many people who inject drugs — subject to criminalisation, stigma and pervasive societal narratives about their 'worth'. Bibi speaks of institutional mind-sets as: 'Ah, a drug addict,

she's inferior and somehow deserves it [illness]'. This casts care as a privilege: 'I can help you, but now you have to be grateful!'. As Rhodes et al. (2013) write: 'gratitude speaks to powerlessness; an inclusion by exception rather than expectation'.

Changes in drug regimens are unlikely to affect perceptions of treatment deservedness unless the resources for meaningful peer involvement and advocacy at all stages of the HCV treatment journey are also provided. Training peers to support HCV treatment provision and employing them in HCV treatment services sends powerful messages regarding trust and worth — not only to the individuals involved, but to the larger community. Trained peers are uniquely placed to advocate for the rights of people who inject drugs and provide support at all stages of the HCV treatment journey. Alec speaks of the unmet need for this input at his service:

> *It would be really good to have someone sit down with you and talk to you, you know, just in a peer mentoring way, that would be great for anyone … it could be someone like, who's been through the treatment themselves, who can connect on a different level.*

Peer-involved and peer-led services can help to engage those who are reluctant to draw on traditional services. This is particularly pertinent for women who use drugs, for whom stigma, criminalisation and attendant fear of child removal create additional barriers to access. Abby, whose children were permanently removed by social services, remarks:

> *They [women] suffer in silence, they just buy it [methadone] on the street… do what they can to survive. And then there's the fear if they've got kids. That's one of the big issues, it's their kids.*

Conclusion

Current innovations in hepatitis C treatment are reflected in a discourse of hope and expectation, with references to 'viral elimination' increasingly noted in policy and academic literature (Watts, 2014; Grebely, 2013). This sense of hope and expectation is not, however, reflected in the narratives of many people who inject drugs. Drug user activists and commentators drawing on the 'HIV treatment as prevention' experience have expressed concern that an increased impetus on hepatitis C 'treatment as prevention' might threaten harm reduction 'prevention as prevention' initiatives such as opioid substitution treatment and needle and syringe programmes (Australian Injecting and Illicit Drug Users League, 2014; Harris et al., 2015; Lazarus et al., 2014). These harm reduction initiatives are already fragile: politically unpopular, under-resourced and, in some countries, such as the United Kingdom, increasingly undermined by a 'recovery agenda' that prioritises abstinence (Home Office, 2010). In many countries in Europe the situation is more acute, particularly in Eastern Europe and Eurasia, where interventions such as opioid substitution treatment can be limited or prohibited.

In order for these fears to be allayed and HCV treatment access to become an entitlement rather than an exception for people who inject drugs, there is a need for supportive and enabling environment, treatment and policy interventions to sit alongside drug development. While interferon-sparing or interferon-free regimes promise more efficacious treatment with a limited side-effect profile, it is important that this does not lead to complacency regarding uptake. Social structural issues including criminalisation, stigma, homelessness and inflexible service provision are likely to continue to impede treatment contemplation and access, however efficacious the treatment (Harris and Rhodes, 2013). Although a complete overhaul of drug policy will not be realisable in the short term, there is a fundamental need for enabling community interventions with meaningful peer involvement in HCV treatment service provision and advocacy. This can aid an investment in and 'owning' of the virus and its treatment by community groups, such as seen in the early days of HIV activism. Continued investment in, and scaling up of, harm reduction interventions such as opioid substitution treatment and needle and syringe programmes is not only an important support for people who inject drugs, but necessary if 'HCV elimination' is ever to become a reality.

Integrated services that are flexible and responsive to the needs of people who inject drugs are key to encouraging HCV treatment access, uptake and completion — particularly in the context of limited community mobilisation. Help with pressing concerns, such as acute health care, can facilitate treatment contemplation. Trust in at least one provider — aided by continuity of care — can facilitate HCV treatment engagement. Community provision of HCV testing and treatment, under the same roof as housing, benefit and primary health support, can facilitate access. This ideally would involve visits by a local hepatologist to the community setting for initial assessment appointments, with the remainder of care being nurse-led. Developments in HCV pharmaceuticals might see treatment provision diversified — available at pharmacies and in other community-based settings.

Service providers that are able to provide a broad range of services for people who inject drugs, such as harm reduction and acute health care, are particularly well placed to introduce information and access to HCV testing and treatment. Not all people who inject drugs, however, feel safe to access services where they may be identified as a drug user. This has ramifications not only for HCV treatment uptake, but also for harm reduction and acute health care access, and it is here that there is the greatest need for enabling environment interventions.

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7

CHAPTER 7

A framework for evaluating scale-up of hepatitis C virus treatment as prevention for people who inject drugs

Daniela De Angelis, Matthew Hickman, Peter Vickerman and Sharon Hutchinson

The availability of new, highly effective, interferon-free direct-acting antiviral drugs has refocused the attention on treatment strategies to reduce the burden of liver disease associated with infection with hepatitis C virus (HCV).

In principle, there are two possible strategies to achieve this goal. The first is to concentrate on the treatment of infected individuals at the initial stages of severe liver disease, for example those with METAVIR liver fibrosis stage F3 (no sign of cirrhosis) or stage F4 (cirrhosis), with the aim of slowing progression and preventing serious morbidity. The second strategy, which we consider here, is to use treatment as a prevention tool. By inducing a reduction in infectiousness in key risk groups, primarily people who inject drugs, treatment leads to a reduction in HCV transmission, an eventual decrease in advanced disease and, importantly, potential control of the HCV epidemic.

Evaluation of HCV treatment as a prevention tool

Results from a number of mathematical modelling papers (e.g. Martin et al., 2011, 2013a,b, 2015; Innes et al., 2014; and others cited in Chapter 4) have raised the expectation that a moderate level of HCV treatment among people who inject drugs could lead to a significant reduction in the prevalence and incidence of HCV infection. It is hypothesised that an HCV treatment strategy would be especially effective if provided in combination with other primary interventions, such as opioid substitution treatment and needle and syringe programmes, by reducing the risk of spread by removing individuals who have been successfully treated from 'the pool of infected'.

However, these studies, which use models appropriately parameterised to reflect epidemic-specific information, remain theoretical. It is acknowledged by the modellers that reality is more complex, and real-world evidence of the impact of scaling up HCV treatment is lacking. Apart from important considerations of how to deliver case-finding and treatment scale-up in practice over time (dealt with, in part, in Chapter 2), the issue of how to assess impact or measure the outcome (i.e. the prevalence and incidence of HCV infection among people who inject drugs living in the community) still needs to be resolved. Parallels can be drawn with the analogous problem for HIV and lessons can be learnt from the HIV experience.

The HIV experience

The problem of evaluating effectiveness of public health interventions has been recurrent in the field of HIV research for some years. The discussion started with the need to assess the impact of initiatives to change sexual behaviours in developing countries (see, for example, Coates, 2008), and more recently the debate has been extended to the consideration of antiretroviral therapy as prevention, namely as a means of reducing transmission and eventually eliminating HIV (HIV Modelling Consortium Treatment as Prevention Editorial Group, 2012). Evidence from the HIV Prevention Trial Network 052 (HPTN 052) (Cohen et al., 2011, 2012) that antiretroviral therapy can greatly reduce HIV transmission between partners in stable HIV-discordant couples, has stimulated the development of models (see Eaton et al., 2012, for a review) suggesting that an expanded

antiretroviral therapy programme would have a variety of benefits at population level, including elimination of HIV within a short timescale. The question of how to assess intervention benefits remains, however, controversial. In principle, three different approaches to evaluation have been explored or suggested: mathematical modelling (Hallett et al., 2009; Awad and Abu-Raddad, 2011; Pickles et al., 2013; Garnett, et al., 2014), ecological studies (Das et al., 2010; Montaner et al., 2010) and cluster randomised trials (Hayes et al., 2011).

Mathematical modelling

Mathematical transmission models are an important tool to evaluate, by simulation, the potential implications of an intervention on disease acquisition and spread. However, they may be of more limited value when it comes to 'attributing' effects to any particular potential intervention programme. They have been commonly used to obtain 'counterfactuals' by simulating scenarios of no intervention, and to derive estimates of effects by comparing the observed and simulated counterfactual outcomes (Garnett et al., 2011). For example, such an approach has been recently employed to assess the strength of evidence for the impact on HIV transmission of a large-scale behavioural intervention in key populations in southern India (Boily et al., 2013; Pickles et al., 2013). It is recognised, however, that this type of model crucially relies on important simplifying assumptions, including assumptions about model structure and parameterisation, often driven by lack of information on the various features of the phenomenon being modelled. So, for instance, the chosen structure may fail to capture aspects of reality necessary to explain observed outcomes (Eaton et al., 2012). Alternatively, model outputs might be sensitive to parameterisation, resulting in alternative explanations for the observed patterns and, consequently, a reduced ability to estimate accurately the effectiveness-related parameters and to identify attributions robustly.

Cluster randomised controlled trials

Cluster randomised controlled trials are the gold standard for the estimation of intervention effects in infectious diseases (Hayes et al., 2000). They allow the capture of both direct effects at the individual level and indirect effects in the population in terms of a reduction in disease, due to an intervention-induced reduction in the risk of infection (herd immunity). The implementation and the interpretation of cluster randomised controlled trials are not without challenges. In the case of HIV treatment, for example, exposure to the intervention will depend on the ability to identify infected individuals through screening, to ensure they access treatment, and that they are compliant. At the analysis stage, any biases affecting any of these steps need to be understood and accounted for to avoid misleading conclusions. Equally important are the duration of follow-up needed to allow for the time delay in the manifestation of some outcomes and the potential for time-varying confounders deriving from both behavioural changes and natural epidemics dynamics (Hayes et al., 2011).

The POPART intervention trial involves a combination of increased HIV screening, immediate antiretroviral therapy (irrespective of baseline CD4 count) in those testing positive and other primary interventions (such as male circumcision, providing condoms and early treatment of other sexually transmitted infections). The trial is currently being carried out in 21 study clusters in Zambia and South Africa, with the main outcome, HIV incidence, measured over the study period in a population cohort of 2 500 individuals randomly selected from each cluster. The assessment of the intervention is based on the comparison of HIV incidence in the population cohort across the three study arms, receiving the full POPART combination package, a reduced version of the POPART package and standard HIV care (Hayes et al., 2014). The motivation for such a trial has been the promising evidence from the HPTN 052 trial and modelling exercises (Cori et al., 2014) and will provide a valuable insight into both the substantive problem of evaluating interventions to reduce HIV and the feasibility of conducting this type of study.

POPART concerns a generalised epidemic in developing countries, with the intervention being administered to the general population. Modelling studies, similar to that in Cori et al. (2014), exist for people who inject drugs and equally suggest that early treatment of HIV in would reduce disease transmission (Degenhardt et al., 2010). However, no evaluation project analogous to POPART has been undertaken in this hard-to-reach population from which we can learn whether a study of this type is at all feasible.

Ecological studies

Some studies have reported an association between uptake of antiretroviral therapy and surrogate measures of HIV transmission. For example, ecological correlations between community measures of HIV viral load and the incidence of HIV infection in Vancouver were interpreted as evidence that antiretroviral therapy could reduce HIV transmission among people who inject drugs (Wood et al., 2009). However, concurrent decreases in the

incidence of HCV infection suggest that injecting risk may also have decreased, and it is possible that this, rather than the scale-up of antiretroviral therapy, could explain the decrease in the incidence of HIV infection. Limitations of ecological studies in assessing the population-level effects of using antiretroviral therapy as a prevention tool are recognised (Smith et al., 2012; Wilson, 2012). These 'natural experiments' can provide valuable evidence, but could also provide misleading results if not interpreted appropriately. Suitable methodologies need to be employed to analyse the resulting data, taking into account the observational nature of these studies. Related issues are discussed in general in guidance issued by the UK Medical Research Council (MRC, no date).

Implications for HCV

The question is how relevant the HIV experience is for HCV in developed countries. HCV treatment has one distinct advantage over HIV treatment: duration of treatment is comparatively short and results in high rates of viral clearance. However, in contrast to the HIV generalised epidemic in Africa, HCV transmission in developed countries is mainly driven by the risk in people who inject drugs.

Similarly to HIV, model projections for HCV have provided a theoretical guidance on the conditions for the successful implementation of a treatment intervention. So, for instance, HCV prevalence is likely to fall more rapidly in populations in which the level of chronic HCV infection is at or below 40 %, and even more so if the prevalence is not more than 20 % (Chapter 4). In the case of HIV, the POPART trial represents the best opportunity to rigorously address the treatment as prevention issue, so would it be possible to adopt a similar design to address the same issue for HCV?

There are a number of important aspects and sources of uncertainty that need to be fully addressed, particularly if the outcomes are changes in the prevalence and/or incidence of HCV infection. These are discussed individually below.

Quantification of the population 'at risk'

The injecting drug population is a 'mixture population' of individuals at risk of acquiring and transmitting infection, encompassing current injectors and those who are in treatment or prison or have recently ceased injecting and are at high risk of relapse. Existing estimates of injecting drug use prevalence rarely capture the whole population at risk; they typically refer to active injectors and exclude those who have temporarily ceased injecting, leading to a potential underestimation of the true prevalence. In most European countries up-to-date estimates are not available (Chapter 1), and those that are available are notoriously uncertain (Jones et al., 2014; Martin et al., 2015) and are often dependent on the methodology used to derive them. For instance, the estimated size of the drug-injecting population that was active in Scotland in 2003 has varied from 19 000 to 27 000 (King et al., 2009) and in England in 2005 from 130 000 to 200 000 (De Angelis et al., 2009; Hay et al., 2009; Harris et al., 2012). However, knowledge of the size of the drug-injecting population is essential for 'treatment as prevention' trials, as estimation of the number of people who inject drugs who are chronically infected with HCV and the derivation of the treatment rates required to reduce HCV transmission to specific levels depends on this information. Inevitably, therefore, as its uncertainty is reflected in all these related quantities, trial designs will become more complex (Hayes and Moulton, 2009).

Baseline and outcome measures: HCV prevalence and incidence

Any trial of HCV treatment requires the baseline prevalence of chronic infection and incidence consistently estimated at relevant locations over any potential trial period.

However, direct measures of the prevalence of HCV antibodies (and of chronic HCV infection) among people who inject drugs do not exist. Surveillance systems necessarily cover only very specific subgroups, are not representative of the drug-injecting population and provide a multiplicity of pieces of information that, if used individually, lead to biased estimates of prevalence. In these circumstances, linking and combining the various sources of data while accounting for the biases can be a viable way of producing meaningful estimates. The problem is compounded if the intervention is implemented in relatively small geographical areas, as in this case paucity of information will add a further complication, increasing the uncertainty of relevant estimates.

An example of this type of linkage and data synthesis is recent work conducted in Scotland. There, by combining data from the Scottish drugs misuse database, the HCV diagnoses register (Shaw et al., 2003), the Needle Exchange Surveillance Initiative (Allen et al., 2012) and a capture–recapture study on a recently infected population (Overstall et al., 2014), it has been possible,

through a Bayesian evidence synthesis, to derive estimates of HCV (antibody) prevalence among people who inject drugs by age group and gender in the Greater Glasgow and Clyde area and in the rest of Scotland (Prevost et al., 2015). A similar exercise in a smaller geographical area would provide local estimates of HCV prevalence, which would constitute the necessary baseline information if a 'treatment as prevention' strategy were to be evaluated in Scottish Health Boards, for instance. Clearly, the issue of uncertain baseline prevalence of HCV remains and could jeopardise the assessment of the significance in a change in prevalence as consequence of the intervention.

Information on the incidence of HCV infection is even more crucial to the evaluation of the impact of an intervention on transmission, yet incidence is even more difficult to quantify as an outcome, particularly if what is needed are estimates at local level and, perhaps, over time. Estimation would have to rely on community surveys of people who inject drugs, with the consequent associated biases (Mills et al., 2012), and on laboratory reporting of recent (incident) infections diagnosed in routine testing, which are also likely to be biased.

Given all the potential biases and uncertainty in the measurement of incidence, it will be very difficult to detect any difference in incidence as a result of the intervention, unless such difference is substantial and the trial is powered appropriately.

Opioid substitution treatment and needle and syringe programmes as time-varying covariates

HCV treatment may act synergistically with other interventions, such as opioid substitution treatment and needle and syringe programmes, which could either enhance or decrease the impact of HCV treatment on the outcome (Martin et al., 2013a). These factors, not controlled for at randomisation, could change over time (in terms of scaling up or even disinvestment) and interact with the intervention, and will need to be measured and incorporated into the analysis.

Other factors: heterogeneity in injecting risk/ potential selection biases

People who inject drugs who are at high risk for infection as a result of their injecting practices, for example, may be more likely to transmit HCV and less likely to enter HCV treatment than those considered at low risk. If the low-risk population is preferentially treated, then HCV treatment may have a lesser impact on HCV transmission. In certain circumstances targeting high- or low-risk injectors maybe more efficient (De Vos et al., 2015). Modelling work suggest that if the level of change from high- to low-risk behaviours is modest, then there will be little or no dilution of the effect of any HCV treatment intervention (Martin et al., 2013a). Ongoing monitoring of the characteristics of the treated populations, any injecting relapse and reinfection rates will be required to test these hypotheses.

Final remarks

It is possible that the complexities in the definition of the injecting drugs population and in outcome measures could preclude the use of cluster randomised controlled trials, particularly if information across multiple sites is needed. This would be particularly a challenge at a European level, given the diversity of both epidemiology and the information available. In addition, the cost of a cluster randomised controlled trial (in terms of HCV drugs) might not be sustainable.

Alternatively, it could be justifiable to conduct non-randomised studies in sites where the drug-injecting population can be well characterised through comprehensive surveillance systems and drug users treated for HCV infection, whether in specialised services or elsewhere, can be adequately followed up.

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Conclusions

Isabelle Giraudon, Dagmar Hedrich, Roland Simon and Paul Griffiths

People who inject drugs are a main target group for HCV treatment

With over 5 million people chronically infected with the virus, it is self-evident that hepatitis C virus (HCV) infection must be regarded as a major threat to public health in the European Union. Moreover, even while noting the gaps that exist in the available data, and the fact that the epidemiological situation varies considerably between countries, it is also clear that in Europe the health burden accruing from HCV infection is disproportionately high among people who inject drugs. Furthermore, there is strong evidence of on-going and, in some countries, high levels of transmission among young injectors, suggesting that infection is acquired relatively early in an individual's injecting career. Effective EU public health strategies to tackle HCV infection and its long-term consequences must have a primary focus on people who inject drugs and those who have acquired HCV through injecting.

It is also of note that the recognition of this problem and its long-term implications is relatively new. The hepatitis C virus was identified for the first time in 1989, but it had already been spreading among injecting drug-using populations in Europe for years. As people who have contracted the virus often remain symptom-free for many years, the problem remained a 'hidden' epidemic until relatively recently, with most cases of infection going undiagnosed and untreated. Today, the importance and potential costs, both to those infected with this disease and in respect to the future impact on health budgets, are now becoming more widely recognised. Despite this, however, overall there has been a failure to develop responses that have managed to impact on the levels of infection among people who inject drugs.

New treatments have removed barriers

Until relatively recently, the main treatment option for HCV infection was to use a combination of the antiviral drugs interferon and ribavirin. This can be effective, but these drugs are often poorly tolerated, have severe side effects and the duration of treatment is relatively long; both factors that are disadvantageous for encouraging uptake. In addition, substantial barriers to access often existed for people who inject drugs; for example, some clinical guidelines required long periods of abstinence before treatment could commence. Moreover, for those who were eligible, pathways into treatment were often difficult to find, with coordination between specialist drug services and medical services addressing hepatitis care often not being optimal. This situation is now changing, however. To a large extent, this has been driven by the introduction over the last few years of new medications, direct-acting antivirals, which can be administered over much shorter periods and with relatively fewer side effects. Thus, there is now a possibility of achieving better treatment retention and outcomes for drug users, with research evidence showing that investments in HCV treatment, even for those who continue to inject drugs, is justified on public health grounds.

Not only has this led to a greater recognition of the need for joined-up approaches between services working with drug problems and those addressing hepatitis, it has also extended the possibilities of how care can be offered. This is because, in many respects, the provision of HCV treatment has become less challenging. The use of all-oral, interferon-free HCV treatment regimens makes them less complex to administer and, therefore, more appropriate to use in primary care, prison and drug treatment settings. This is helpful, as a recognised element of good practice in the delivery of HCV care for people who inject drugs is close collaboration between the different specialist services involved. There is now a growing experience of developing improved care pathways, and the potential health gains of more effective working in this area appear considerable.

Taken as a whole, these developments now mean that, probably for the first time, a real opportunity exists to tackle the high prevalence of HCV infection at the level of injecting drug-user communities and thereby make a significant impact on the HCV problem in Europe.

Preventing further infections

Europe is not homogenous with regard to levels of drug use and injecting, nor with regard to the prevalence of infectious diseases among drug-using populations. Moreover, levels of injecting and associated risk behaviour can change over time. Recent HIV outbreaks have shown, for example, that patterns of use can be highly variable, and that they can be influenced by other factors like the emergence of new psychoactive substances on the drugs market. Any future increase in injecting drug use has the potential to be associated with increasing the risks of new HCV infections. Health promotion activities are, therefore, needed to discourage people from injecting drugs, or to change their behaviour in order to reduce the risk of contracting the virus if they do inject. Measures that have been shown to reduce reported injecting risks, such as the adequate provision of clean injecting equipment and opioid substitution treatment for dependent opioid users, remain key elements in current prevention approaches in this area. However, coverage of both measures remains suboptimal in many countries and, therefore, requires strengthening, not only because of potential health gains in the area of HCV, but also because they deliver health benefits elsewhere. Extending services availability to the most chronic, disadvantaged and vulnerable groups, such as those in housing need, is likely to be particularly important, as these individuals may be at greater risk and more difficult to attract to mainstream services. Beyond this, however, the experience to date would suggest that without the additional component of HCV treatment, it will be difficult to impact significantly on HCV infection rates at the population level. The challenge, therefore, is to develop a comprehensive approach to care that ensures that both HCV prevention activities and treatment access are adequately resourced and proactively delivered.

Diagnosing those infected

The fact that many of those infected with HCV are unaware of their infection status has consequences for the continued transmission of the virus at population level and for the long-term health of the individuals concerned. A need remains, therefore, to raise both public and professional awareness in order to encourage those at risk to come forward for testing, and for services to be more proactive in offering testing. An important caveat here is that testing needs to be accompanied by appropriate follow-up and referral mechanisms to facilitate access to treatment for positive cases. It is not, however, just current injectors who may be unaware of their infection status, as those who have ever injected are at risk, even if the behaviour has been discontinued. Targeted case-finding and public information campaigns may also, for this reason, be of value to encourage former injectors to come forward for testing.

Monitoring infection rates is also important, as it can provide crucial feedback on the effectiveness of current interventions and indicate where more resources are needed. This represents another strong argument for point-of-care testing as a routine element of the health service response. In conclusion, offering testing to all drug users in care can be regarded as part of good practice in this area. This is supported by the newly agreed EU minimum quality standards for demand reduction (Council of the European Union, 2015), which recommend that 'treatment services provide voluntary testing for blood-borne infectious diseases, counselling against risky behaviours and assistance to manage illness'. In addition to offering screening at drug services, there is some evidence to support a more proactive approach by extending this provision via community-based outreach approaches. The high prevalence of those with drug problems within the criminal justice sector also means that offering voluntary testing in prisons and other places of confinement is important. Wherever screening is provided, follow-up assessment will also need to take into account other factors that may increase the risk of positive cases progressing to severe liver damage, including age at infection, gender, alcohol use and co-infection with infectious agents, such as the human immunodeficiency and hepatitis B viruses.

The need for greater treatment access and referral pathways tailored to the needs of people who inject drugs

The potential long-term social and economic costs associated with HCV infection are considerable, with European countries facing escalating healthcare costs if infected populations progress into severe liver disease. Epidemiological modelling studies suggest that the combination of widespread hepatitis C treatment, supported with other primary prevention measures, has the potential to reduce HCV transmission to low levels. The model projections provide strong theoretical evidence for the hypothesis that hepatitis C treatment, if scaled up sufficiently, can reduce the prevalence of HCV infection and that treating people who inject drugs is likely to be cost-effective. There is now a need for more empirical data and evaluations of the impact of scaling

up hepatitis C treatment among people who inject drugs in order to demonstrate how health gains in this area may become manifest. Studies that look at how to improve responses in areas such as HCV case-finding and treatment in prison are likely to be particularly important. Scaling up of treatment offers will require the development of effective working partnerships between specialist services working with drug users and those offering HCV treatment and care. In the past, referral pathways for drug injectors into specialist hepatitis care have represented a critical weak link in this area. This is now changing, and good practice models have been developed. There remains, however, a need for these to be extended, and this is an area in which guidelines and clinical practice standards have an important role to play. Given the pace of change in respect to the availability of new pharmacotherapies, it will be necessary to regularly review and adapt guidance in this area to new opportunities that are likely to become available.

International collaboration to support ambitious hepatitis elimination policies

The opportunities offered by the emergence of direct-acting new antiviral drugs have been recognised by the World Health Organization, which has declared the elimination of viral hepatitis as a public health threat by 2030 as one of its global strategic objectives (WHO, 2016). This is an ambitious but achievable objective. The greatly improved prospects for treating viral hepatitis have quickly been translated into new testing and treatment guidance, national planning toolkits and economic and burden of disease modelling tools. Indicators to monitor and report progress at global and national level have now also been adopted. The draft WHO action plan for the health sector response to viral hepatitis in the European Region, currently under discussion, contains a number of milestones and targets specific to people who inject drugs. Once the WHO action plan is adopted, the EMCDDA is committed to working with our international, European and national partners in this area to ensure that progress is monitored effectively and to support the measures necessary to ensure that the ambitious public health goals established for the elimination of HCV infection are realised.

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Hepatitis C among drug users in Europe: epidemiology, treatment and prevention provides a timely contribution to raising awareness of the hepatitis C epidemic in Europe and the opportunities now opening up to tackle this problem decisively. A state-of-the-art review of the epidemiology of hepatitis C virus (HCV) infection in Europe and an overview of the way preventive measures are currently implemented in European countries set the scene. International experts address the treatment of HCV infection among people who inject drugs, with an emphasis on how we encourage uptake and deliver effective outcomes. Implementation issues are also explored, as are the complementary roles of treatment and prevention. The new medicines and treatment regimens driving the transformation in the HCV treatment landscape are reviewed in detail. The challenges of scaling up HCV treatment and successfully involving drug-using patients is explored from different viewpoints, including that of the drug user.

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