European Monitoring Centre
for Drugs and Drug Addiction

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PERSPECTIVES ON DRUGS

Hepatitis C treatment for injecting drug users

Transmitted through the sharing of needles, syringes and other injecting equipment, hepatitis C is the most common infectious disease among people who inject drugs in Europe today. In this analysis, the EMCDDA looks at some of the positive advances in treating the disease, including a new generation of medicines.

A hidden epidemic of hepatitis C

Hepatitis C is the most common infectious disease in people who inject drugs, among whom it is usually transmitted through the sharing of injecting equipment such as needles and syringes. Most of those who become infected go on to develop chronic HCV infection, which can lead to severe health problems in individuals and place a major burden on health care systems. Yet hepatitis C is both preventable and curable, and the development of new medicines to treat hepatitis C, has made rapid progress with several new medications obtaining marketing authorization in 2014 and 2015.

Hepatitis C virus (HCV) infection is highly prevalent among people who inject drugs across Europe, with national infection levels for this group ranging from 14 % to 84 %. However, infected individuals often show no noticeable symptoms, and many are unaware that they are carrying the virus, leading to it being referred to as a 'hidden' epidemic. People who inject opioids in Europe constitute an ageing population, which includes many who have been living with hepatitis C for 15 to 25 years. The natural history of chronic hepatitis C virus infection (cirrhosis risk escalates after 15 to 20 years) and the ageing cohort effect in this population mean that a large burden of advanced liver disease can be expected over the next decade.

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emcdda.europa.eu/topics/pods/hepatitis-c-treatment

Reducing infections among injecting drug users

Among people who inject drugs, the sharing of needles and syringes is the key risk factor for acquiring HCV infection, although there is also considerable evidence of a potentially high risk of infection associated with sharing drug-

preparation equipment such as cookers, filters, swabs and water (Pouget et al., 2012). However, there is good evidence to show that retention in opioid substitution treatment reduces injection frequency (Gowing et al., 2008), and that it is most effective in reducing HCV transmission when used alongside interventions that support safer injection practices (Hagan et al., 2011). Two studies that examined the independent and combined effects of needle and syringe programmes and opioid substitution treatment on HCV incidence concluded that the combined effect of these two interventions resulted in the greatest reductions in HCV transmission (Turner et al., 2011; Van Den Berg et al., 2007).

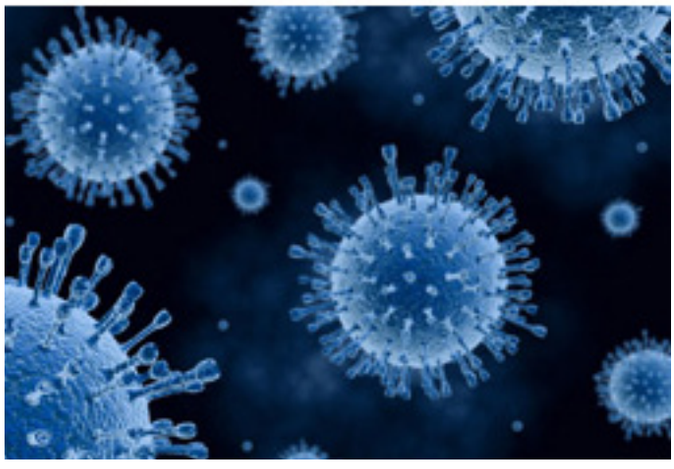
However, modelling studies have been used to explore the potential effectiveness of different hepatitis C interventions, and these indicate that it may be difficult for opioid substitution treatment and high-coverage ([1]) needle and syringe programmes alone to substantially reduce the overall hepatitis C prevalence among people who inject drugs. For example, modelling the scale-up of both interventions for the United Kingdom (with 40 % baseline chronic hepatitis C prevalence among the target population) shows that they are only likely to lead to substantial reductions in the prevalence of chronic hepatitis C after 10 years, if both of these interventions cover 80 % or more of the injecting population (Vickerman et al., 2012). Such high coverage levels may be difficult to sustain over periods.

Hepatitis C treatment as prevention

Recent advances in hepatitis C treatment approaches, including the development of new molecules called direct-acting antivirals (DAA) and the introduction of interferon-free treatment regimens show much promise (see box 'Current treatment and new hepatitis C medicines), including the potential for treating hepatitis C among people who inject drugs. In this area, modelling studies suggest that hepatitis C treatment could play an important role in preventing the spread of the virus. A study by Martin et al. (2014) projecting the impact of current and scaled-up treatment on chronic HCV prevalence in a range of seven UK sites with varying prevalence levels indicated that an absolute reduction in hepatitis C prevalence of at least 15 % might be achieved over 10 years as a result of treating 26 infections per year per 1 000 people who inject drugs with relative reductions ranging from 12 % to 86 % after 10 years.

Barriers to accessing hepatitis C treatment

In spite of recent improved treatment outcomes for hepatitis C patients, available data show treatment uptake continues to be very low among injecting drug users. The literature highlights



a number of possible reasons for this. Service providers cite concerns around adherence, risk of exacerbation of psychiatric disorders and the potential for reinfection after treatment as reasons for not assessing or treating hepatitis C in injecting drug users (Edlin et al., 2001; Soriano et al., 2002). On the part of patients, the lack of access of people who inject drugs to testing still constitutes a key-barrier to entering a care pathway. In addition, poor knowledge about hepatitis C and treatment availability, the absence of noticeable symptoms (Grebely et al., 2011) and the perceived side-effects of treatment (Swan et al., 2010) are named as barriers for accessing hepatitis C care. Finally, until recently, current drug injecting was an exclusion criterion for receiving government-funded hepatitis C antiviral treatment in a number of European countries. This obstacle, however, is now being removed, with most clinical guidelines revised to allow for the treatment of hepatitis C in injecting drug users.

Strategies to improve treatment and care

A number of the lessons learned in responding to the HIV epidemic can be transferred to reducing the spread of hepatitis C among people who inject drugs, including recognition of the importance of putting in place a set of comprehensive, coordinated and multidisciplinary responses. Advocacy groups in Europe have highlighted the need to develop HCV services. In particular, the need for strategies to reduce the burden of HCV among people who use drugs, including improved access to HCV testing, treatment and care services, and the scaling-up of community-based and harm reduction interventions. The enhancement of treatment uptake is important for people who inject drugs and effective treatment options need to be available and easily accessible for this population group. The co-location of hepatitis C treatment and opioid substitution treatment is likely to facilitate user access, and might also be linked with mental health care. Improving treatment adherence among people who inject drugs is another area where improvements can be made and the use of case management, support services

([1]) Where injecting drug users receive on average one or more sterile syringes for each injection reported.

and provider education and training to improve health- and HCV-literacy among PWID and service providers are likely to enhance care.

Conclusion

This analysis draws attention to the high levels of HCV infection among people who inject drugs, both as an urgent public health priority, and as a field that has recently seen major advances in medical interventions. If hepatitis C treatments for people who inject drugs are to be effective, they will need to be embedded in and delivered as part of a comprehensive package of interventions. An important area for future investigation will be to review the uptake of hepatitis C treatment among people who inject drugs, and identify and challenge any barriers that prevent them from receiving an adequate and equitable service.

Interactive element: video

Video: hepatitis C treatment among injecting drug users available on the EMCDDA website: emcdda.europa.eu/topics/pods/hepatitis-c-treatment

Facts and figures

Hepatitis C is a liver disease caused by the hepatitis C virus (HCV)

The incubation period for hepatitis C ranges from as little as **2** weeks to 6 months

Following initial infection with HCV, approximately **80 %** of people do not exhibit any symptoms

In **25 %** of liver cancer patients, the underlying cause is hepatitis C

Approximately 130–**150 million** people worldwide have chronic HCV infection (WHO, 2014)

Between **14 % and 84 %** of injecting drug users in Europe are infected with HCV

About 75–85 % of newly infected individuals develop chronic disease and 60–70 % of those with chronic HCV infection develop chronic liver disease; **5–20 %** develop cirrhosis and 1–5 % die from cirrhosis or liver cancer

Current treatment and new hepatitis C medicines

The goal of HCV treatment is to achieve a sustained virological response (SVR), which is defined as undetectable HCV RNA six, and lately three, months after cessation of therapy, leading to HCV clearance (Wendt et al., 2014; Martinot-Peignoux et al., 2010). SVR corresponds to a definitive cure of HCV infection in more than 99 % of cases (Swain et al., 2010) and is associated with improved outcomes regarding HCV-related liver disease, including fibrosis, cirrhosis, cancer and death. Until recently, the standard hepatitis C treatment has been injectable pegylated interferon (PEG-INF) alpha (interferon is an immunomodulating protein that interferes with viral replication; in pegylated form it lasts longer in the body) combined with oral ribavirin (RBV), an antiviral medication, so-called PEG-INF-RBV therapy (PR). However, treatment with interferon has several and even some life-threatening side effects and is poorly tolerated by some patients (WHO, 2014; EASL, 2014a).

Scientific advances have led to the development of new antiviral drugs for hepatitis C, which are much more effective, safer and better-tolerated than existing therapies. These therapies, known as oral directly acting antiviral agent (DAAs) therapies simplify hepatitis C treatment by significantly decreasing monitoring requirements and by increasing cure rates (WHO, 2014). Direct-acting antiviral agents target particular stages in the life cycle of the virus in order to prevent it replicating.

There are two main areas of research in this field. The first is concerned with drugs or therapies, known as protease and polymerase inhibitors, which block particular enzymes crucial for the viral lifecycle. The second area is looking at drugs that interfere with the genetic structure of the virus. Research is currently being carried out into inhibitors that can interrupt the activity of the enzymes linked with the replication of the hepatitis C virus. The launch of first-generation protease inhibitors in 2011 provided major advances for genotype 1 patients, the most common of the six HCV genotypes. Two first-wave, first-generation protease inhibitors, telaprevir and boceprevir were approved for use in combination with PR in patients infected with HCV genotype 1 and are recommended in clinical guidelines (e.g. NICE 2012a; 2012b; EASL 2014a). Treatment results show increased SVR rates by 30 % for naïve patients, and even more for treatment-experienced genotype 1 patients who were relapsers to previous PR treatment (Wendt et al., 2014; Bacon et al., 2011).

But things are changing rapidly and there are many new hepatitis C medicines in the pipeline, often showing promising results in phase II and III clinical trials. New hepatitis C treatments have entered or are about to enter the markets, which improve on the older treatment regimes in a number of ways. They can be taken orally rather than injected; they are taken once a day rather than two times a day or more; the side effects of the medication are significantly reduced; treatment is of a shorter duration; and there are many fewer drug-drug interactions.

In January 2014 , sofosbuvir, an inhibitor that interrupts the activity of the enzyme polymerase, used for hepatitis C virus replication, became the first all oral treatment medication for hepatitis C in combination with ribavirin to be given marketing authorisation by the European Commission. This was followed by new triple-therapy options, allowing for short duration, interferon-free and ribavirin independent regimens for genotype 1 and 4 patients by combining sofosbuvir with two other DAAs, which entered the market in May (simeprevir) and August 2014 (daclatasvir) (EASL, 2014b). In November 2014, EU regulators granted authorization for a once-daily single tablet treatment regimen, combining sofosbuvir with ledipasvir, a highly potent anti-retroviral across genotypes. Depending on prior treatment history and cirrhosis status, duration of treatment is reduced to 12 to 24 weeks. The medication, indicated for genotypes 1 and 4 patients - including those with HIV co-infection - achieved SVR rates of 94 % to 95 % twelve weeks after completing therapy even without ribavirin (ION-I, ION-II and ION-III trials; see Medscape slideshow http://www.medscape.com/features/slideshow/ion). In January 2015, a so-called 3D all-oral combination of DAAs (paritaprevir/ritonavir-ombitasvir-dasabuvir) that can be used with or without ribavirin was approved by the European Commission (paritaprevir-ritonavir-ombitasvir-dasabuvir), adding another 12- to 24-week treatment option for HCV genotype 1 patients.

Various combinations using DAAs showed high rates of sustained virological response (~95 %). Importantly, high cure rates were also demonstrated in patients with previous treatment failures, decompensated cirrhosis and hepatitis C recurrence after transplantation, making it clear that the interferon era is over (not so clear for ribavirin, which might still have a role in difficult-to-treat populations) (Lodoño et al., 2014).

Eliminating the need for interferon injections and with reduced treatment durations, it is hoped that the new regimens will both increase the uptake and facilitate the retention in treatment for people who inject drugs (PWID). Despite these outstanding developments, which have created high expectations of curing the disease in more than 90 % of patients, data from real-life cohorts evaluating the new antiviral combinations on a longer-term basis are still needed. Furthermore, the costs of antiviral medicines remain high – potentially presenting a barrier for individuals wishing to initiate or continue hepatitis C treatment.

The possibility of developing a therapeutic vaccine, which would prevent the development of chronic HCV infection following repeated exposure, is feasible and being investigated, although a long way off at present, according a recent review (Grebely et al., 2012)

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