JIM Original Article

doi: 10.1111/joim.12740

Treatment as Prevention for Hepatitis C (TraP Hep C) – a nationwide elimination programme in Iceland using direct-acting antiviral agents

S. Olafsson[1,2], T. Tyrfingsson[3], V. Runarsdottir[3], O. M. Bergmann[1], I. Hansdottir[3,4], E. S. Björnsson[1,2], B. Johannsson[5], B. Sigurdardottir[5], R. H. Fridriksdottir[1], A. Löve[2,6], M. Hellard[7,8,9], T. J. Löve[2,10], T. Gudnason[11], M. Heimisdottir[2,12] & M. Gottfredsson[2,5,10]

From the [1]Division of Gastroenterology and Hepatology, Landspitali University Hospital; [2]Faculty of Medicine, School of Health Sciences, University of Iceland; [3]SAA – National Center of Addiction Medicine; [4]Faculty of Psychology, School of Health Sciences, University of Iceland; [5]Division of Infectious Diseases; [6]Division of Virology, Landspitali University Hospital, Reykjavik, Iceland; [7]Centre for Population Health, Burnet Institute, Melbourne; [8]Department of Epidemiology and Preventive Medicine, Monash University, Clayton; [9]Department of Infectious Diseases, Alfred Hospital, Melbourne, VIC, Australia; [10]Department of Science, Landspitali University Hospital; [11]Chief Epidemiologist, Directorate of Health; and [12]Division of Finance, Landspitali University Hospital, Reykjavik, Iceland

Abstract. Olafsson S, Tyrfingsson T, Runarsdottir V, Bergmann OM, Hansdottir I, Björnsson ES, Johannsson B, Sigurdardottir B, Fridriksdottir RH, Löve A, Hellard M, Löve TJ, Gudnason T, Heimisdottir M, Gottfredsson M (Landspitali University Hospital; University of Iceland; SAA – National Center of Addiction Medicine; University of Iceland; Landspitali University Hospital, Reykjavik, Iceland; Burnet Institute, Melbourne; Monash University, Clayton; Alfred Hospital, Melbourne, VIC, Australia; Landspitali University Hospital; Directorate of Health Landspitali University Hospital, Reykjavik, Iceland). Treatment as Prevention for Hepatitis C (TraP Hep C) – a nationwide elimination programme in Iceland using direct-acting antiviral agents. *J Intern Med* 2018; **283**: 500–507.

A nationwide programme for the treatment of all patients infected with hepatitis C virus (HCV) was launched in Iceland in January 2016. By providing universal access to direct-acting antiviral agents to the entire patient population, the two key aims of the project were to (i) offer a cure to patients and thus reduce the long-term sequelae of chronic hepatitis C, and (ii) to reduce domestic incidence of HCV in the population by 80% prior to the WHO goal of HCV elimination by the year 2030. An important part of the programme is that vast majority of cases will be treated within 36 months from the launch of the project, during 2016–2018. Emphasis is placed on early case finding and treatment of patients at high risk for transmitting HCV, that is people who inject drugs (PWID), as well as patients with advanced liver disease. In addition to treatment scale-up, the project also entails intensification of harm reduction efforts, improved access to diagnostic tests, as well as educational campaigns to curtail spread, facilitate early detection and improve linkage to care. With these efforts, Iceland is anticipated to achieve the WHO hepatitis C elimination goals well before 2030. This article describes the background and organization of this project. *Clinical trial number: NCT02647879.*

Keywords: direct-acting antiviral agents, elimination, hepatitis C, intravenous drug use, policy, prevention.

Introduction

Hepatitis C virus (HCV) infection is one of the leading causes of cirrhosis and hepatocellular carcinoma (HCC) worldwide [1]. Injection drug use (IDU) is the main mode of transmission in developed countries, accounting for the majority of new and existing infections [2]. In recent years, a growing number of new direct-acting antiviral (DAA) agents have become available, revolutionizing treatment for HCV. These new agents are highly efficacious, have limited side effects and allow shorter duration of treatment than previously available medications [3]. However, treatment uptake remains low in most countries, partly because of high drug costs, particularly when they

initially came on to the market, but also because of barriers to care amongst people who inject drugs (PWID). If treatment uptake remains low, DAAs are likely to have minimal impact on reducing the incidence and prevalence of HCV infection [4].

Much attention has been given recently to the concept of treatment as prevention for HCV [5, 6]. Experience from HIV treatment shows that antiretroviral therapy not only limits long-term complications for those infected but also lowers their likelihood of infecting others [7]. In contrast to HIV, HCV is curable with relatively short course of DAAs. Therefore, in the absence of an effective vaccine against the virus, treatment as prevention for HCV may provide an opportunity for preventing onward transmission and reducing the prevalence of the disease and its sequelae. Modelling work has suggested that even by a modest scale-up of treatment uptake amongst PWID, a significant reduction in prevalence can be achieved [6]. Consequently, HCV elimination using a treatment as prevention approach combined with harm reduction efforts is considered attainable; WHO has set elimination targets for hepatitis C, including a 65% reduction in HCV-related deaths and 80% reduction in HCV incidence by 2030 [8]. Some countries – including Georgia, Australia, Egypt, Portugal and Spain – are also currently undertaking national hepatitis C elimination efforts [9]. Iceland is an ideal setting to examine the effectiveness of the treatment as prevention approach in a real-world setting. Results from recent mathematical modelling for Iceland suggest that by intensifying harm reduction, as well as diagnostic and treatment efforts, the WHO targets for HCV elimination could be achieved sooner than 2030, in fact even 6–10 years earlier [10]. This study describes the approach taken to achieve this goal.

Study setting and epidemiology of hepatitis C in Iceland

Iceland has a population of 340.000 – covered by national health insurance [11]. It is a high-income country with healthcare expenditure amounting to 8.9% of GDP in 2014 [12, 13]. Iceland's only university hospital (Landspitali University Hospital, LUH), located in Reykjavik, serves as a tertiary and quaternary referral centre for the country and runs its only virology laboratory. The majority of PWID seek services and addiction treatment at Vogur Hospital, SAA – National Center of Addiction Medicine (Society of Alcoholism and other Addiction, SAA). Access to treatment for addiction is good [14] reflected by the fact that 7.5% of the living population in Iceland over 14 years old have been admitted to Vogur Hospital, SAA, for addiction treatment [15, 16]. SAA routinely screens all patients with history of IDU for HCV. In Iceland, it is mandatory to report all HCV antibody diagnoses to the Chief Epidemiologist. A registry of all diagnosed cases of HCV has been kept since 1991.

Over the past 20 years, 40–70 new cases of HCV have been diagnosed in Iceland every year (Fig. 1) [17]. Assuming a viraemic rate of 80% amongst antibody-positive individuals, the total HCV viraemic population in 2014 can be estimated to include 1100 (estimated range, 880–1300) individuals, corresponding to a viraemic population prevalence of 0.3% (0.3–0.4%) [18]. The vast majority of people with HCV infection in Iceland have a history of IDU [19].

The most commonly used drug amongst PWIDs in Iceland has been the prescription drug methylphenidate, which is indicated for the treatment of attention deficit disorders [20, 21]. However, majority of PWIDs treated at SAA use more than one substance intravenously [22]. The prevalence of HCV antibody amongst people who have ever injected drugs is estimated at 45%, but amongst people who have injected for a year or more, it is almost 70% [22]. The most common HCV genotypes are 3a (55%) and 1 (43%) [18].

Background of Trap Hep C in Iceland

The possibility of a nationwide HCV treatment/elimination programme was discussed in November 2014 by physicians managing HCV-infected patients in Iceland and representatives of the pharmaceutical company Gilead. The idea was to offer DAAs to all HCV-positive patients within an entire population within a relatively short time frame and simultaneously initiate an observational study with long-term follow-up. Gilead would, in a study setting, provide DAAs free of charge for the project. Upon approval of relevant parties in Iceland (the Ministry of Health, Landspitali University Hospital, Vogur Hospital – SAA and the Chief Epidemiologist), formal preparation for a nationwide elimination programme was initiated, led by a team of physicians at Landspitali University Hospital. Detailed clinical guidelines, a research protocol and a practical project plan was drawn up, covering staffing, equipment and other resources required.

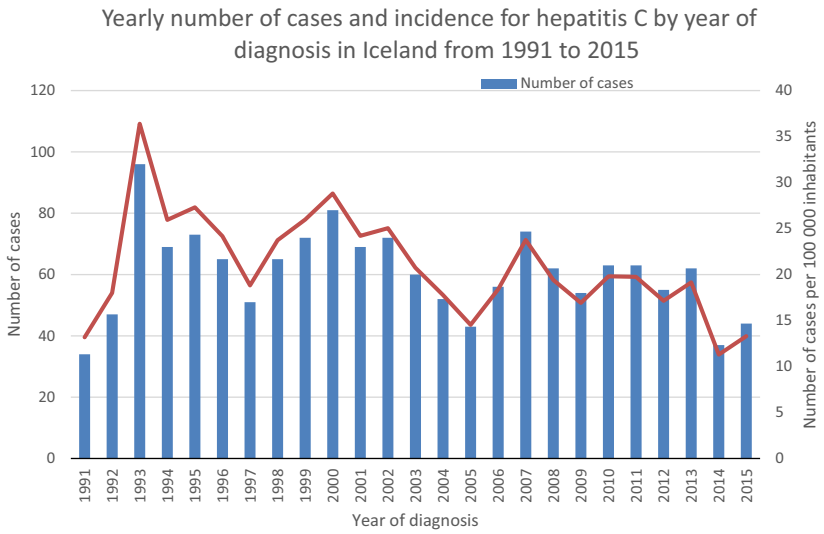

Fig. 1 *Epidemiology of Hepatitis C in Iceland, 1991–2015. Yearly number of cases (left-hand y-axis) and annual incidence per 100.000 inhabitants/year (right-hand y-axis), irrespective of the country of transmission. Graph based on data from the Chief Epidemiologist, Directorate of Health, Iceland.*

Another team was responsible for working with Gilead Sciences Inc. to create a contractual agreement for the project. Under this agreement, signed in December 2015, Gilead provides DAAs in an epidemiological study setting for a limited time (36 months) for all HCV-positive individuals covered by the Icelandic health insurance system. The Icelandic government provided special funding for the overall organization of the project, diagnostic tests and other services related to the nationwide elimination campaign. The project was named 'Treatment as Prevention for Hepatitis C in Iceland' or 'TraP HepC' – to underline the fact that active PWID, who are most likely to spread the virus, would be the focus of the treatment effort.

TraP HepC research protocol

To measure the short-term and long-term effects of TraP HepC, the incidence of HCV infection acquired in Iceland and the incidence rates of cirrhosis and HCC due to HCV will be monitored for up to 15 years (Fig. 2). Additional factors, such as virological response rates, compliance, and prevalence amongst PWID, are monitored as well. Use of healthcare services and costs of treatment will be tracked. These data as well as the data generated during the project will be used to assess the effect of the intervention on the future burden of illness for patients and society. Informed consent is obtained for each patient participating in the study. Those who choose not to participate in the research arm of the project are nevertheless offered the same treatment and services. For consenting subjects, study data will be extracted from electronic patient records. The initial (treatment) phase of the research will be monitored by a clinical research organization. The study is registered at clinicaltrials.gov (trial number NCT02647879).

Main participating organizations and their roles

Landspitali University Hospital serves as a project centre. The main collaborator of LUH is SAA. The Chief Epidemiologist, on behalf of the Ministry of Health, supervises the project. The project has a general steering committee, as well as a research steering committee.

Patient management and priority groups

The core of the treatment programme is based on collaboration between two medical specialties at LUH (infectious disease, hepatology) and the third, addiction medicine, at SAA.

TraP HepC is based on a multidisciplinary team approach, where physicians, nurses, psychosocial

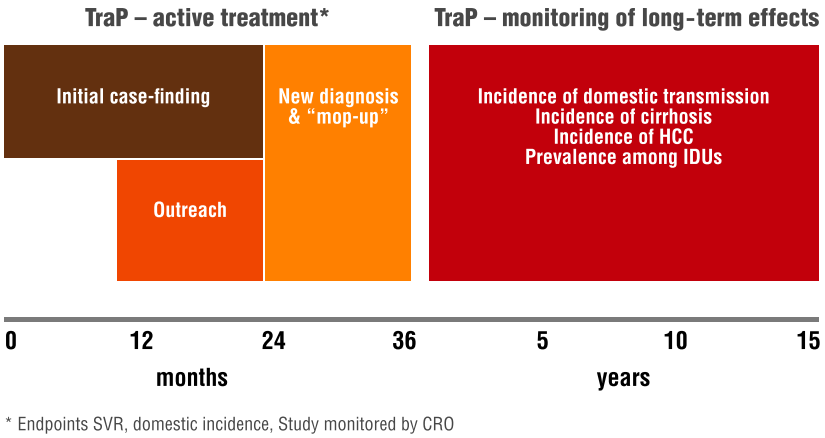

Fig. 2 *Phases and timing of TraP HepC in Iceland. The active treatment phase (brown, orange and yellow columns) will last 36 months. Starting with initial case finding and treatment of patients with HCV infection which is already known, during the first 24 months. Outreach will start after 12 months or earlier in select cases such as prisons. After the first 24 months of active treatment, the focus will shift to new diagnosis and 'mop-up' of new cases of HCV in addition to remaining cases identified by the Chief Epidemiologist. Relapses and reinfections will be treated during the entire 36-month period. The endpoints for the first 36-month phase of the project include recruitment, completion of treatment, sustained virological response (SVR), and prevalence in certain key populations. This part of the project will be monitored by a Clinical Research Organisation (CRO). Monitoring of long-term effects of the TraP HepC project (red column) will ensue immediately following the active treatment phase; here, the incidence of domestic transmission will be monitored as well as long-term complications from chronic HCV infection for up to 15 years. It is important to note that the different components of TraP HepC may overlap.*

support services (including shelters for the homeless) and the penitentiary system in Iceland are all involved. The initial evaluation and ongoing care for the majority of patients take place in one of the three main treatment sites, two at LUH and one at SAA. In addition, evaluation and treatment are provided by the TraP HepC staff members through outreach in prisons, homeless shelters and other locations as deemed necessary. Treatment is offered to HCV-positive individuals who are covered by the Icelandic health insurance. All prison inmates are offered HCV testing and subsequent treatment if infection is confirmed. To reduce the risk of re-infection, treatment is initiated simultaneously for all infected inmates in the initial treatment phase. If released from the prison whilst on treatment, prisoners are followed at one of the TraP HepC treatment sites.

The overall aim was to treat the majority of HCV-positive individuals within two years from the start of the programme, using the third year to 'mop-up' any missed or incident cases (Fig. 2). Emphasis is placed on early case finding and treatment for (i) active PWID with HCV viremia, (ii) those at highest risk for progression to cirrhosis or severe complications and (iii) inmates of the penitentiary system.

Patient recruitment

Using a dynamic compartmental model of HCV transmission, it has been estimated that an 80% reduction in domestic incidence is achievable in Iceland by the years 2025 and 2020 if a minimum of 75 of 1000 and 188 of 1000 PWID are treated per year, respectively [10].

Patients are identified using cross-referencing of four data sources: LUH's virology laboratory system, LUH's administrative data sets (ICD diagnoses), the hepatitis C registry and SAA's database, which contains comprehensive data on IDU and virological test results for all patients admitted for addiction treatment. Patients are contacted by TraP Hep C staff members and informed of the ongoing treatment programme and the therapeutic options available and encouraged to visit one of the three treatment sites. Patients living outside Reykjavik are offered travel bursary, and in some cases, patients are evaluated and treatment initiated in their hometown. Furthermore, to enhance clinical awareness, letters of notice were sent to all physicians in Iceland at the launch of the project and regularly thereafter. In addition, in an effort to reach out to those who may be at risk for infection

but have not been diagnosed information has been made available to patients through media outlets such as web pages, social media and information leaflets, which are sent to every home in the country. Patients can contact the programme via e-mail and a toll-free number to register for counselling, testing and treatment.

Rapid testing is offered in select sites, including shelters.

Evaluation, treatment and monitoring

It has been estimated that by offering treatment to up to 200 patients every 4 months, the majority will be treated within the first two years of the programme (Fig. 2). Interview, laboratory work (including virological tests) and hepatic elastography (Fibroscan®) are generally undertaken at the baseline visit. A mobile Fibroscan® is available for incarcerated patients and others unable to visit the treatment centres. Qualifying patients start treatment according to the guidelines within four weeks and preferably within two weeks of their initial workup. Patients are interviewed by a physician at the initial (baseline) and final visits (following HCV PCR testing at 12 weeks posttherapy). Most other interviews are conducted by nurses. In the programme, DAAs are prescribed by specialists in addiction medicine, hepatology and infectious disease.

Electronic patient record subsystem – remote access

Patient data are entered at the point of care directly into an electronic patient record (EPR) using a customized interactive module. Data are recorded and stored in the EPR using the patient's personal ID number. This module of the EPR is designed to support structured data entry (most data are entered in numerical or coded format). A list of the personal ID numbers of those participating in the research project will be used to extract study data from the EPR for inclusion in a separate de-identified study database.

Treatment regimens

During the initial phase (from January to October 2016), all patients were treated with ledipasvir/sofosbuvir (Harvoni®), in most cases for 8–12 weeks, with patients with genotype 3 also receiving ribavirin (Table 1). From November 2016, all patients have been treated with sofosbuvir/velpatasvir (Epclusa®, Table 2). Patients who have a contraindication for these agents have access to other treatment regimens.

Approach to PWID

Methods to optimize adherence include on-treatment monitoring, pill boxes, increased nurse counselling and support, linkage to other relevant health services (e.g. addiction treatment, psychiatric services), travel stipends for those living outside Reykjavik and incentives, such as prepaid mobile phone cards. Harm reduction education and counselling are provided in the context of treatment. PWID are encouraged to bring their friends and injection partners for testing and treatment with the aim of treating injecting partners simultaneously to decrease the risk of re-infection [23].

Table 1 *Most common initial treatment regimens for chronic HCV in Iceland, from January to October 2016, according to the Icelandic treatment guidelines*

GT 1,4,5,6		
TN, noncirrhotic	LDV/SOF	Viral load <6 million IU/mL, 8 weeks (GT 1 only)
TN, noncirrhotic	LDV/SOF	Viral load >6 million IU/mL, or non-GT-1, 12 weeks
TN, cirrhotic	LDV/SOF	12 weeks
TE, noncirrhotic	LDV/SOF	12 weeks
TE, cirrhotic	LDV/SOF+RBV	12 weeks (24 weeks if no RBV)
Decompensated/post-transpl	LDV/SOF+RBV	12 weeks (24 weeks if no RBV)
GT 3		
TE or cirrhosis	LDV/SOF+RBV	24 weeks (24 weeks if no RBV)
TN	LDV/SOF+RBV	12 weeks (24 weeks if no RBV)

IU, international units; GT, genotype; TN, treatment-naïve; TE, treatment-experienced; LDV, ledipasvir; SOF, sofosbuvir; RBV, ribavirin; HCV, hepatitis C virus.

Table 2 *Most common initial treatment regimens for chronic HCV in Iceland, from November 2016 onwards, according to the Icelandic treatment guidelines*

GT 1,2,3,4,5,6		
TN, TE, cirrhotic, noncirrhotic	SOF/VEL	12 weeks
Decompensated cirrhosis	SOF/VEL+RBV	12 weeks (24 weeks if no RBV)

GT, genotype; TN, treatment-naïve; TE, treatment-experienced; VEL, velpatasvir; SOF, sofosbuvir; RBV, ribavirin; HCV, hepatitis C virus.

Harm reduction

A formal collaboration has been established with The Icelandic Red Cross, which runs a mobile harm reduction unit, providing a needle-syringe-programme (NSP) in the capital city, Reykjavik. Furthermore, collaboration has been established with pharmacies where needles and syringes can be obtained at a very low cost to lower barriers for PWID. The estimated annual number of clean needles and syringes provided to each injection drug user in Iceland is 430.

Sterile injecting instruments and prepackaged 'kits' are offered to PWID seeking services at LUH and SAA. There is also interest in providing NSP within the penitentiary system and this is under consideration. In Iceland, PWIDs with opiate addiction have had access to opioid substitution treatment (OST) since 1999, most commonly buprenorphine/naloxone (Suboxone®). Currently, a total of 120 patients are receiving OST treatment, run by SAA – the National Center of Addiction Medicine. However, the absence of pharmacological substitute treatment for stimulant users, which comprise the majority of active PWID in Iceland, remains a challenge.

Intensified screening efforts

An important component of TraP HepC is an intensified screening of risk groups. The use of point-of-care testing (rapid tests) for HCV and HIV is applied to approach patient populations that are difficult to reach, such as those visiting homeless shelters, halfway houses and the mobile harm reduction unit. Screening has been increased at emergency rooms, addiction treatment centres, within the penitentiary system and at other relevant locations. Public awareness campaigns in the mass media focus on people at risk who have not yet sought testing.

Monitoring of re-infections

As successful antiviral therapy does not confer subsequent immunity to HCV, re-exposure to the virus can lead to re-infection. Screening and repeat referral will continue for all risk groups (including PWID) at the time of healthcare contact, for example when they seek care in emergency rooms or when admitted to addiction treatment centres. Practicing clinicians are encouraged to order HCV and HIV tests amongst PWID if prior tests were taken more than 6 months ago. The incidence of re-infections will also be monitored by offering all patients previously treated and cured to have their HCV RNA measured 12 months post-treatment.

Initial treatment results

In the real-world setting of Iceland fifteen months after launching the TraP HepC, 557 individuals have been evaluated (68% males, 32% females), comprising 56–70% of the estimated total number of viraemic patients. Thereof, treatment has been initiated for 526 patients, 363 LDV/SOF-based, 162 SOF/VEL-based and 1 other regimen. The mean age is 42 years and at the time of baseline evaluation 37% of the patients reported IDU in the past 6 months. Virological response rates are generally high; however, individuals who are homeless were less likely to achieve sustained virological response (SVR) at 12 weeks (74% compared to 94%, $P = 0.0005$) and those who report current IDU are also significantly less likely to achieve SVR at 12 weeks (87% compared to 95%, $P = 0.003$) [24]. No serious adverse events have been reported.

Pitfalls and challenges

There are several potential challenges facing the TraP HepC initiative. Visitors from abroad, such as tourists, temporary workers, immigrants, incarcerated and asylum seekers, with pre-existing chronic

HCV infections, may facilitate or maintain transmission of the virus during their visit to Iceland. For example, there are HIV transmission clusters in Iceland, which are known to have originated in Eastern Europe [25]. In addition, the number of workers from foreign countries as well as tourists has increased dramatically in Iceland over the past five years [26, 27]. Coinciding with this, the police authorities have expressed their concern for an increase in the sex trade [28, 29]. It is also known that unprotected sexual activity amongst men who have sex with men (MSM) in Europe is on the rise, which goes hand in hand with increased incidence of sexually transmitted infections, including HIV, syphilis and HCV [30–32]. It should be noted, however, that all immigrants and asylum seekers from outside the European Union are screened for HCV in Iceland within weeks from arrival and those who immigrate are offered treatment as part of their health insurance coverage. International travel, most likely, is uncommon amongst active PWID, due to limited financial means. However, travel amongst Icelandic MSM for the purpose of sex may be quite common although limited data exist on this [33].

The long-term continued access to DAA's, screening for HCV and harm reduction programmes, will be dependent on continued political support once the current financial support by the Ministry of Health and provision of DAA's by Gilead comes to an end. Successful elimination of the disease might reduce the sense of urgency and vigilance towards protection, detection and treatment of hepatitis C amongst those at risk. On the other hand, successful elimination based on the treatment approach of this project might strengthen political support for maintaining high access to both DAA's and effective screening for HCV as well as other resources needed for prevention, harm reduction and treatment.

Summary and conclusions

In summary, with the TraP Hep C programme, Iceland is taking a cohesive, multipronged approach that includes scale-up of prevention, testing and early treatment of hepatitis C in both hospital and community settings. It includes a multidisciplinary public health model of care and cooperation between government, health services, the penitentiary system and community organizations. Although some parts of this programme are empirical in nature and highly dependent on intangibles, such as vigilance and motivation amongst healthcare professionals and the public alike, it is hoped that treatment as prevention will lower the incidence and morbidity associated with HCV well in advance of the WHO targets. The results of Icelandic project will provide important data and inform others globally trying to achieve the WHO hepatitis C elimination goals.

Conflict of interest statement

Sigurdur Olafsson: Speaker's fee from Merck. Magnus Gottfredsson: Speaker's fee from Astellas and Gilead. MH and the Burnet Institute receive investigator-initiated research funding from Gilead Sciences, AbbVie and BMS. All other authors: No reported conflict.

Acknowledgements

Gilead provides DAAs free of charge for the project.

References

1 Global Burden of Disease Study. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; **388:** 1545–602.
2 Nelson PK, Mathers BM, Cowie B *et al.* Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet* 2011; **378:** 571–83.
3 Feld JJ, Jacobson IM, Hezode C *et al.* Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med* 2015; **373:** 2599–607.
4 Sibley A, Han KH, Abourached A *et al.* The present and future disease burden of hepatitis C virus infections with today's treatment paradigm – volume 3. *J Viral Hepat* 2015; **22 (Suppl. 4):** 21–41.
5 Hellard M, Doyle JS, Sacks-Davis R, Thompson AJ, McBryde E. Eradication of hepatitis C infection: the importance of targeting people who inject drugs. *Hepatology* 2014; **59:** 366–9.
6 Martin NK, Vickerman P, Grebely J *et al.* Hepatitis C virus treatment for prevention among people who inject drugs: modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology* 2013; **58:** 1598–609.
7 Cohen MS, Chen YQ, McCauley M *et al.* Antiretroviral therapy for the prevention of HIV-1 transmission. *N Engl J Med* 2016; **375:** 830–9.
8 World Health Organisation. WHO Global hepatitis report 2017. http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua=1
9 Lazarus JV, Wiktor S, Colombo M, Thursz M; EASL International Liver Foundation. Micro-elimination – a path to global elimination of hepatitis C. *J Hepatol* 2017; **67:** 665–6.
10 Scott N, Ólafsson S, Gottfreðsson M *et al.* Modelling the elimination of hepatitis C as a public health threat in Iceland: a goal attainable by 2020. *J Hepatol* 2017; https://doi.org/10.1016/j.jhep.2017.12.013. [Epub ahead of print].

11 Statistics Iceland. Statistical series 29. http://www.statice.is/publications/publication-detail?id=56760. ISSN: 1670-4770. June 2016;101.2017
12 The Central Bank of Iceland. Economy of Iceland. http://www.cb.is/publications/publications/publication/2016/10/13/Economy-of-Iceland-2016/: The Central Bank of Iceland; 2016
13 Statistics Iceland. Statistical Yearbook of Iceland 2015 [cited 2017 23.06.2017]. Available from: https://issuu.com/hagstofa/docs/landshagir2015_1bb8919b88d9b6?e=7193385/31693918.
14 Hansdottir I, Runarsdottir V, Tyrfingsson T. Addiction treatment in Iceland. In: el-Guebaly N, Carrà G, Galanter ME, eds. *Textbook of Addiction Treatment: International Perspectives*. 2. Italia: Springer Verlag, 2015; 1199–209.
15 Tyrfingsson T, Thorgeirsson TE, Geller F *et al.* Addictions and their familiarity in Iceland. *Ann N Y Acad Sci* 2010; **1187:** 208–17.
16 National Center of Addiction Medicine. Annual Report 2016. Available from: https://saa.is/wp-content/uploads/2017/02/Ársrit_skýrsla_18022017_an_crop.pdf.
17 Chief Epidemiologist Iceland. Tilkynningarskyldir sjúkdómar. http://www.landlaeknir.is/smit-og-sottvarnir/smitsjukdomar/tilkynningarskyldir-sjukdomar/. 2016.
18 Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *Lancet Gastroenterol Hepatol* 2017; **2:** 161–76.
19 Fridriksson B, Bergmann OM, Olafsson S. Treatment of hepatitis C with peginterferon and ribavirin in Iceland from 2002–2012. *Laeknabladid* 2017; **103:** 125–8. [In Icelandic].
20 Bjarnadottir GD, Haraldsson HM, Rafnar BO *et al.* Prevalent intravenous abuse of methylphenidate among treatment-seeking patients with substance abuse disorders: a descriptive population-based study. *J Addict Med* 2015; **9:** 188–94.
21 Indridason H, Gudmundsson S, Karlsdottir B, Love A, Briem H, Gottfredsson M. Long term nationwide analysis of HIV and AIDS in Iceland, 1983–2012. *J AIDS Clin Res* 2014; **5:** 1000387.
22 Samtök áhugamanna um áfengis-og vímuefnavandann. Ársrit SÁÁ. https://saa.is/wp-content/uploads/2017/02/A%CC%81rsrit_to%CC%88lur_18022017_an_crop.pdf2016 [in Icelandic]
23 Hellard M, Rolls DA, Sacks-Davis R *et al.* The impact of injecting networks on hepatitis C transmission and treatment in people who inject drugs. *Hepatology* 2014; **60:** 1861–70.
24 Gottfredsson M, Tyrfingsson T, Runarsdottir V *et al.* Increased intensity of testing and treatment for elimination of hepatitis C. Real world experience from the Treatment as Prevention (TraP HepC) program in Iceland. *Hepatology* 2017; **66:** number 1 (suppl). Abstract 1135.
25 Sallam M, Esbjornsson J, Baldvinsdottir G *et al.* Molecular epidemiology of HIV-1 in Iceland: Early introductions, transmission dynamics and recent outbreaks among injection drug users. *Infect Genet Evol* 2017; **49:** 157–63.
26 Statistics Iceland. External migration by citizenship: statistics Iceland; 2017. Available from: http://statice.is/statistics/population/migration/external-migration/
27 Statistics Iceland. Passengers through Keflavik airport: statistics Iceland; 2017. Available from: http://statice.is/statistics/business-sectors/tourism/passengers/.
28 Tourism pushing up demand for sex workers in Iceland: Iceland Monitor; 2017. Available from: http://icelandmonitor.mbl.is/news/politics_and_society/2016/04/13/tourism_pushing_up_demand_for_sex_workers_in_icelan/.
29 Prostitution on the rise in Iceland: Iceland Review online; 2017. Available from: http://icelandreview.com/news/2017/05/11/prostitution-rise-iceland.
30 Jansen K, Schmidt AJ, Drewes J, Bremer V, Marcus U. Increased incidence of syphilis in men who have sex with men and risk management strategies, Germany, 2015. *Euro Surveill* 2016; **21:** https://doi.org/10.2807/1560-7917.ES.2016.21.43.30382. [Epub ahead of print].
31 van Santen DK, van der Helm JJ, Del Amo J *et al.* Lack of decline in hepatitis C virus incidence among HIV-positive men who have sex with men during 1990–2014. *J Hepatol* 2017; **67:** 255–62.
32 Martin NK, Thornton A, Hickman M *et al.* Can hepatitis C virus (HCV) direct-acting antiviral treatment as prevention reverse the HCV epidemic among men who have sex with men in the united kingdom? epidemiological and modeling insights. *Clin Infect Dis* 2016; **62:** 1072–80.
33 European Monitoring Centre for Drugs and Drug Addiction. Travel and drug use in Europe: a short review. 2017. Available from: http://www.emcdda.europa.eu/publications/thematic-papers/travel_en.

Correspondence: Sigurdur Olafsson MD, FACP, Department of Medicine, Division of Gastroenterology and Hepatology, Landspitali University Hospital, 101 Reykjavik, Iceland; School of Health Sciences, Faculty of Medicine, University of Iceland, 101 Reykjavik, Iceland. (e-mail: sigurdol@landspitali.is).
and
Magnus Gottfredsson MD, PhD, FACP, Department of Medicine, Division of Infectious Disease, Landspitali University Hospital, 108 Reykjavik, Iceland; School of Health Sciences, Faculty of Medicine, University of Iceland, 101 Reykjavik, Iceland. (e-mail: magnusgo@landspitali.is).

