REMAINING CHALLENGES FOR HEPATITIS C VIRUS ELIMINATION

in the era of direct-acting antiviral agents

CAS ISFORDINK

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Resterende uitdagingen voor hepatitis C virus eliminatie in het tijdperk van direct werkende antivirale middelen
(met een samenvatting in het Nederlands)

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CHAPTER 1

GENERAL INTRODUCTION AND THESIS OUTLINE

GENERAL INTRODUCTION

During the 1970s and 1980s, usually transient increases in transaminases following transfusion of blood products indicated the existence of a blood-borne infective agent causing post-transfusion hepatitis.[1] As the majority of these cases lacked serologic evidence of hepatitis A or B virus infection, the disease was labelled non-A non-B hepatitis (NANBH).[1] An extensive search for the NANBH agent ultimately resulted in the characterization of the hepatitis C virus (HCV) in 1989[2]. Soon thereafter, it was unveiled that HCV was the causative agent of more than 90% of NANBH cases.[1]

HCV is considered a major global health problem, with an estimated worldwide prevalence of chronic infection of 58 million in 2020 and an annual incidence of 1.5 million.[3,4] HCV is an enveloped, single-stranded RNA virus of the genus *Hepacivirus* within the family *Flaviviridae.* The virus genome consists of approximately 9,600 nucleotides, that encode for a polyprotein containing over 3,000 amino acids.[5] Due to the absence of a proofreading mechanism of the viral RNA polymerase, HCV strains frequently mutate and display a high genetic diversity. Currently, the virus is classified into 8 genetically distinct major genotypes (1 t/m 8) and over 86 assigned subtypes (a, b, c, d, etc.).[6–8] Genotype 1 is the most common genotype, accounting for 44% of global HCV infections, followed by genotypes 3 (25%) and 4 (15%).[9]

HCV transmission

HCV is transmitted most efficiently through percutaneous blood-to-blood contact. The most common percutaneous routes of exposure are contaminated medical equipment, blood products, needles for injecting drug use or unsterile tattooing, and occasionally vertical transmission (i.e. transmission from mother to child in utero or during delivery). Additionally, HCV transmission is seen in men who have sex with men (MSM), mainly those with HIV co-infection or using HIV pre-exposure prophylaxis (PrEP; the use of antiviral therapy in individuals at risk of HIV infection that successfully prevents HIV infection but not HCV infection). Transmission of HCV in MSM is multifactorial, as it is associated with high-risk sexual behaviour (e.g. condomless anal intercourse, high number of sexual partners, toys, fisting), injecting drug use before or during sex (i.e. chemsex), and biological factors (HIV co-infection, presence of an ulcerative sexually transmitted infection affecting the mucosal barrier).[10,11] Although HCV RNA can be detected in semen,[12] sexual transmission in HCV serodiscordant, HIV-negative heterosexual couples is very rare regardless of condom use.[13,14]

Natural history of HCV infection

HCV infection regularly has an asymptomatic clinical course and therefore patients are often unaware of their infection. After acute HCV infection, 70-80% of infections progress to a chronic infection (Figure 1).[15,16] Spontaneous clearance of HCV infection usually occurs within six months, with only few cases of spontaneous clearance exceeding one year of infection duration.[17] Several factors are associated with an increased proportion progressing to chronic HCV infection, including HIV co-infection, other immune disorders, and male sex.[18,19]

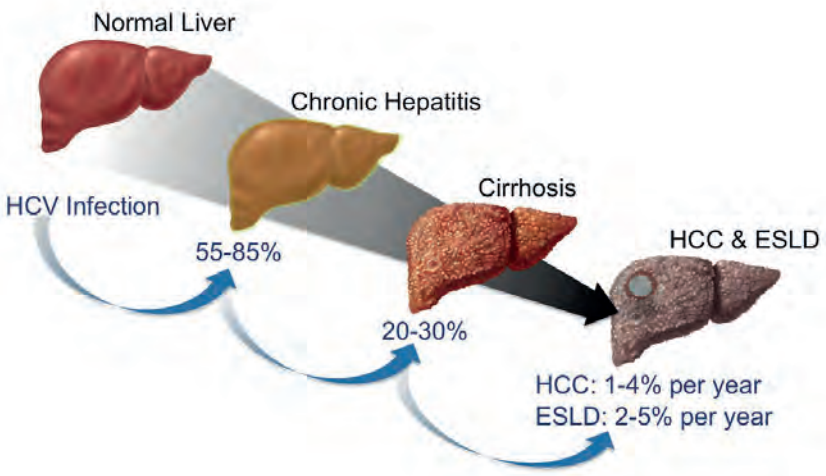

Figure 1. Natural history of HCV infection.
Figure copied from US Department of Veterans Affairs, https://www.hepatitis.va.gov/hcv/background/natural-history.asp [date accessed: 08 July 2022]. Abbreviations: HCV: hepatitis C virus. HCC: hepatocellular carcinoma. ESLD: end-stage liver disease.

After 20 to 30 years of chronic HCV infection, 20-30% of patients develop cirrhosis due to progressive liver fibrosis.[18] Obesity, alcohol use, and hepatitis B virus (HBV) co-infection are associated with an increased rate of fibrosis progression.[20,21] Individuals with cirrhosis have an annual risk of 1-4% of hepatocellular carcinoma and 2-5% of a decompensating event, mainly ascites or gastroesophageal variceal bleeding.[22,23] Additionally, HCV has extrahepatic manifestations such as cryoglobulinemic vasculitis and lymphoma, while HCV is also associated with an increased risk of cardiovascular disease, insulin resistance, chronic kidney disease, and depression.[24–26] Due to all these effects, overall survival of individuals with chronic HCV infection is substantially impaired,[24] with 720,000 global deaths related to HCV in 2013.[27] Furthermore, health-related quality of life of individuals with chronic HCV infection is significantly reduced compared to individuals never HCV-infected.[28,29]

Antiviral therapy

Two years before the discovery of the hepatitis C virus, the first clinical trials to treat NANBH with subcutaneous interferon injections commenced.[30]. These trials initially demonstrated amelioration of transaminases and even liver histology in a large part of treated patients.[30–32] However, interferon-only regimens resulted in definitive cure of chronic HCV infection, as indicated by a sustained virological response (SVR), in only 10-20%.[32] During the 1990s, the addition of the oral antiviral drug ribavirin and later substitution of standard interferon with PEGylated interferon (PEG-interferon) improved HCV treatment efficacy (Figure 2). Nonetheless, treatment was still only successful in 40-50% of cases with genotypes 1 or 4, and 70-80% of cases with genotypes 2 or 3.[33] Furthermore, in individuals with compensated cirrhosis, interferon-based treatment was less effective with an SVR rate of 30-50%.[34] In addition, the burdensome interferon-based treatment had to be given for a period of 6 months to 1 year and had severe side-effects.[35,36]

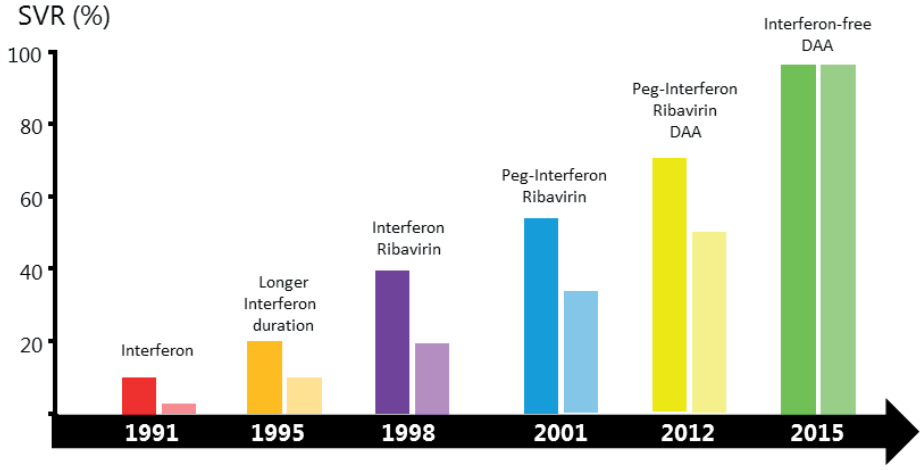

Figure 2. Evolution of HCV therapy since the discovery of the virus in 1989.
Light coloured bars represent treatment efficacy for patients with cirrhosis. Abbreviations: SVR: sustained virological response. DAA: direct-acting antivirals.

This all started to change with the introduction of direct-acting antivirals (DAA). In 2003, a proof of concept study showed an impressive in-vivo HCV RNA reduction following administration of an oral HCV non-structural protein (NS)3 protease inhibitor.[37] Subsequently, it took until 2011 before the long-awaited first-generation protease inhibitors became commercially available in the Netherlands in combination with PEG-interferon and ribavirin. Although this regime still had severe side-effects,

treatment efficacy increased significantly, especially for the most prevalent genotype 1 that responded less to prior therapy. In 2014, all-oral and interferon-free DAA became available for chronic HCV patients with advanced liver fibrosis or cirrhosis, with subsequent universal access since November 2015. Current DAA can be divided into three classes, targeting various key components of the viral genome responsible for viral replication (Figure 3). These are the NS3-4A protease inhibitors (-previr), NS5A inhibitors (-asvir), and NS5B inhibitors (-buvir). Current combinations of these classes are pangenotypic and achieve SVR rates >95% after only eight to twelve weeks of treatment. Furthermore, DAA have only few side-effects and re-treatment of failures again has a comparable success chance.[38]

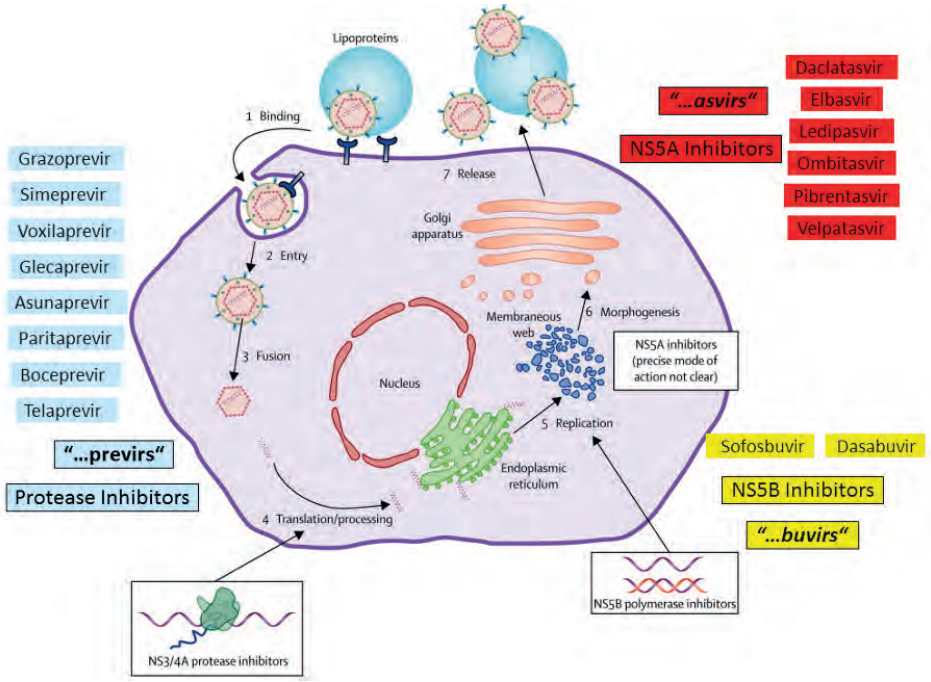

Figure 3. Different classes of direct-acting antiviral agents and their mechanism of action.
Figure adapted from Manns and Cornberg, Lancet Inf Dis 2013[39]. Abbreviations: NS: non-structural protein.

HCV key populations and (micro-)elimination

The advent of DAA prompted the World Health Organization in 2016 to publish their strive for elimination of HCV infection as a public health threat by 2030.[40] In countries with a high HCV prevalence, nationwide screening campaigns successfully identifying many HCV-infected individuals have shown to be effective tools for HCV elimination.[41,42] With an estimated 0.16% of the population ever chronically HCV-infected, the Netherlands

has a low HCV prevalence, corresponding to approximately 23.000 (low estimate 8,000 – high estimate 38,000) individuals.[43] In similar low prevalence settings, general screening campaigns have proven to be less (cost-)effective.[44,45] The favourable approach to HCV elimination in these settings is micro-elimination, the concept of pursuing elimination within specific key populations with a relatively high HCV prevalence.[46] The highest absolute prevalence of HCV infection in the Netherlands is found in first-generation migrants from HCV endemic countries, while the highest relative prevalence is found in people who (formerly) inject(ed) drugs (PWID), MSM living with HIV or using HIV pre-exposure prophylaxis, and people with inherited bleeding disorders, in particular haemophilia.[18,43,47–50]

Migrants from countries with a high HCV prevalence account for a large proportion of chronic HCV infections in the Netherlands.[43,49] These countries are mainly located in Eastern Europe, Africa, and Asia (Figure 4). The highest genetic diversity of HCV strains is observed in Sub-Saharan Africa and Asia, due to centuries-long persistence in the human population and low HCV transmission rates.[51] In contrast, the vast majority of HCV infections in Western Europe and the United States of America (USA) are caused by a limited number of epidemically spread HCV genotypes, mainly 1a, 1b, 2a, 3a, 4a, and 4d. As most DAA trials were executed in Western Europe and the USA, only rarely patients with other HCV genotypes and subtypes were included.[52] More recently, several studies have reported that DAAs might not be as effective against some of these genetically diverse subtypes as they are against epidemic genotypes.[53–55] To advance HCV elimination in low and middle-income countries, confirming the efficacy of DAA in these so-called 'non-epidemic genotypes' is of utmost importance.

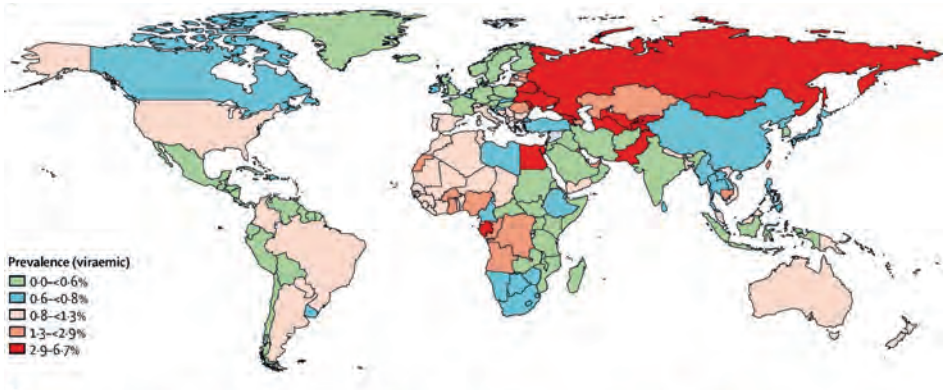

Figure 4. Global prevalence of hepatitis C virus infection
Figure adapted from Polaris Observatory HCV Collaborators, Lancet Gastroenterology & Hepatology, 2017.[9]

The origin of the key population of people who (formerly) inject(ed) drugs can be traced back to the heroin epidemic in the Netherlands that started in the 1970s.[56] Many of these individuals were infected with blood-borne viral infections through the sharing of contaminated needles used for injecting hard drugs, including heroin, cocaine, and amphetamines. During the 1980s and 1990s, harm reduction services including safe needle programs and opioid substitution therapy were introduced, leading to reduced transmission of viral infections between PWIDs.[56] Nonetheless, prevalence of HCV antibodies is very high among PWID and approximately 10% of HCV-positive PWID have an HIV co-infection.[43] Currently, the number of active injecting drug users is low, and the vast majority of the PWID population are thus former injecting drug users. In recent years, injecting drug use has also become more popular among men who have sex with men, who inject drugs before or during sex (i.e. chemsex). In general, this population is not referred to when discussing the PWID key population.

People living with HIV are another HCV key population, with an estimated 2.3 million people living with HIV/HCV globally in 2016.[57] HIV/HCV co-infection is common due to an overlap in the transmission route of both viruses, with high prevalence seen in key populations such as PWID, people treated with non-viral inactivated blood derivates produced from large plasma pools, and men who have sex with men.[18,58,59] Previously, HIV was associated with an accelerated progression of liver fibrosis in people with an HCV co-infection.[60] However, the introduction of effective antiretroviral therapy for the treatment of HIV from 1996 onwards and in recent years the availability of less hepatotoxic antiretroviral treatment options, has resulted in a similar progression of liver fibrosis in HIV/HCV co-infected and HCV mono-infected patients.[61]

Inherited bleeding disorders are a group of hereditary diseases characterized by bleeding tendency due to an absence or deficiency of clotting proteins. The most common inherited bleeding disorders are the X-linked disorders haemophilia A (clotting factor VIII deficiency) and haemophilia B (clotting factor IX deficiency). The mainstay of the treatment of people with haemophilia is infusion of the missing clotting factor. The introduction of cryoprecipitate and later plasma-derived clotting factor concentrates, produced from large pools of blood and plasma, substantially improved the life expectancy and quality of life of these individuals.[62] Unfortunately, blood-borne viral infections such as HIV, HBV, and HCV were spread on a large scale through these plasma-derived products. Additionally, the use of commercial American plasma products made from blood or plasma from paid donors instead of unpaid donor products increased the risk of contaminated batches. In the Netherlands, nearly all persons with severe haemophilia were infected with HCV before the 1990s.[16] As a result, the most common cause of mortality in these individuals is liver-related death,[63] virtually all due to the consequences of chronic HCV infection.[18]

Finally, a group that is rarely mentioned as a target population for HCV micro-elimination is people who are previously diagnosed with HCV infection but are lost to follow-up from HCV care before being cured. This group consists of individuals from all key populations who never attended or stopped attending HCV care for a wide range of reasons, such as a lack of consequence given to a positive HCV test or reluctance to start the burdensome interferon therapy. Several studies in the Netherlands have reported that up to 40% of previously diagnosed HCV patients are lost to follow-up.[64–66] Retrieval and treatment of these patients could be an effective method to halt progression of liver disease in these patients as well as reduce the pool of HCV-viremic individuals and thus reduce ongoing transmission.

Follow-up after HCV eradication

Successful HCV treatment significantly reduces the risk of liver-related complications such as hepatocellular carcinoma and decompensated cirrhosis, both following interferon-based SVR and DAA-based SVR.[67] Nonetheless, a residual risk of liver-related complications remains for patients with advanced liver fibrosis or cirrhosis.[67] Due to the high efficacy of DAA, even in patients with cirrhosis, the vast majority of patients with HCV-related cirrhosis has now achieved SVR. Suboptimal follow-up and management of these individuals might complicate achieving the HCV elimination goal of reducing HCV-related mortality. An important topic in the DAA era is therefore the frequency of liver-related complications post-SVR and the optimal management regarding surveillance of hepatocellular carcinoma and gastroesophageal varices in patients with HCV-related advanced fibrosis or cirrhosis.

THESIS OUTLINE

In this thesis, remaining barriers and challenges for HCV elimination in the era of highly effective HCV therapy are described. **Part I** focuses on challenges for HCV elimination in people with haemophilia. **Chapter 2** is a narrative review describing the history and current situation regarding viral hepatitis in people with haemophilia. In **Chapter 3,** liver-related complications of long-term HCV infection in people with inherited bleeding disorders are reported, mainly focusing on the setting following successful antiviral treatment. In **Chapter 4,** the health-related quality of life of people with haemophilia after successful HCV treatment is described and compared with the quality of life of people with haemophilia who were never chronically HCV-infected.

Part II describes challenges for HCV elimination in people living with HIV. In **Chapter 5**, the prevalence of hepatitis C viremia in people living with HIV in the Netherlands between 2000 and 2019 is described, followed by an analysis of barriers to DAA treatment uptake during unrestricted access. **Chapter 6** is an international cohort study in which DAA uptake during unrestricted access was compared between several countries and factors associated with remaining DAA-untreated over time were analysed. In the European, cross-sectional study reported in **Chapter 7**, data from several cohorts were combined to assess DAA efficacy among individuals with HIV/HCV originating from Sub-Saharan Africa or Southeastern Asia.

Part III concerns challenges for HCV elimination in the Netherlands in general. **Chapter 8** is a nationwide retrieval project aiming to re-engage previously diagnosed but lost to follow-up individuals with care. **Chapter 9 i**s a nationwide study aiming to evaluate DAA efficacy and prevalence of resistance-associated substitutions in patients treated for a non-epidemic HCV genotype in the Netherlands. In **Chapter 10**, current literature regarding liver-related complications following DAA-based HCV eradication in patients with cirrhosis is reviewed and summarised, to determine whether we should continue surveillance for hepatocellular carcinoma and gastroesophageal varices in these patients. **Chapter 11** is a modelling study in which the progress towards HCV elimination in the Netherlands is estimated according to several scenarios.

Finally, the general discussion in **Chapter 12** discusses the current HCV epidemiology in the Netherlands, remaining challenges for HCV elimination in several key populations as well as the Netherlands in general, and policy changes required to advance HCV elimination in the Netherlands.

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PART I

CHALLENGES FOR HEPATITIS C VIRUS ELIMINATION IN PERSONS WITH HAEMOPHILIA

CHAPTER 2

VIRAL HEPATITIS IN HAEMOPHILIA: HISTORICAL PERSPECTIVE AND CURRENT MANAGEMENT

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ABSTRACT

The introduction of clotting factor concentrates has substantially improved the lives of people with clotting factor deficiencies. Unfortunately, the transmission of blood-borne viral infections through these plasma derived products led to a huge epidemic of HIV and viral hepatitis in people with haemophilia (PWH). In a significant proportion of PWH exposed to these viruses, the ensuing decades-long chronic infection resulted in excess morbidity and mortality. Fortunately, developments in safety of blood products, as well as vaccination and highly effective antiviral treatments have improved the perspectives of PWH. This article reviews the background of the viral hepatitis epidemic in PWH, the natural history of hepatitis B and C infections and their long-term management.

Treatment of Haemophilia

Haemophilia A and B are inherited X-linked bleeding disorders due to deficiency of factor VIII (FVIII) and factor IX (FIX) respectively. The mainstay of their treatment is through infusion of the missing clotting factor. Initial methods of replacement were poor and inefficient, involving transfusion of fresh blood or fresh frozen plasma (FFP), products that contain all the clotting factors in a dilute format. A major advance in FVIII replacement was the discovery that cryoprecipitate contained FVIII in concentrated form and was more efficient (in terms of volume) than FFP in treating people with haemophilia A.[1] Problems with cryoprecipitate use, however, include the need to be given in hospital, requirement for storage in a freezer, need for thawing and a high likelihood of allergic reactions. Most of these limitations were overcome by the introduction of plasma derived lyophilised FVIII and FIX concentrates in the 1970s. This enabled the storage of the products in a domestic refrigerator, allowed full treatment in a small volume and made it possible for patients to treat themselves at home, as well as giving them the freedom to travel. In the 1990s recombinant factor concentrates that did not use human plasma were introduced and are the main form of concentrates in use in Europe and North America today.[2] In many parts of the world, however, plasma derived concentrates still predominate as the main form of treatment for PWH.

Transfusion transmitted infection

It has been recognised for more than 80 years that transfusion of blood and blood products could be associated with transfusion transmitted infection (TTI).[3] This remained a relatively small issue until products from multiple donors were pooled and started to be infused in recipients. In the late 1960s reports of jaundice started appearing after cryoprecipitate use in patients with haemophilia. The frequency of post-transfusion hepatitis increased in the 1970s and it was recognised that, whilst many cases were due to hepatitis B, another infective agent termed non-A, non-B hepatitis (NANBH) was involved. In the early 1980s it became clear that the majority of PWH exposed to pooled plasma derived concentrates were infected with NANBH, although its significance was uncertain. At around the same time the human immunodeficiency virus (HIV) became recognised as a major cause of TTI. Transfusion related NANBH was shown in the early 1990s to be almost exclusively due to hepatitis C virus (HCV).[4]

Although HIV and HCV are the most well-known transfusion transmitted viruses, many others have been reported. Patients with haemophilia are susceptible to infection through their plasma derived FVIII or IX concentrate treatment only with viruses that can be found in plasma; they are no more susceptible than the general population to cell associated viruses such as the cytomegalovirus, Epstein-Barr virus and several human herpes viruses, which have leukocytes as their mode of transmission.[5]

Viral Hepatitis and HIV in Haemophilia

The risk of viral hepatitis and HIV transmission was very small with products produced from single donations such as red cells, platelets, fresh frozen plasma or cryoprecipitate. Notably, treatment of a bleeding episode would often require multiple infusions over several days. Furthermore, a single cryoprecipitate treatment required multiple units of cryoprecipitate. Nonetheless, the total number of required individual donations per bleeding episode was still relatively low for these therapies. The major move to treat PWH with lyophilised pooled plasma concentrates changed all that, as the pools of plasma used for fractionation could contain tens of thousands of individual donations. The level of viraemia in HCV- and HIV-infected individuals is very high and, as no natural immunity existed, most batches of FVIII/FIX were infected with HCV and some with HIV as well. The infectivity of specific batches depended on the plasma source, and those relying on volunteer European donors were less infectious (especially for HIV) than batches made by USA manufacturers who collected blood from paid donors using plasma collection facilities sometimes located in prisons or in deprived areas.[6]

The rates of HIV/Hepatitis B virus (HBV)/HCV infections in the haemophilic population varied depending on availability and use of cryoprecipitate vs lyophilised plasma derived concentrate and the use of commercial American plasma sourced products vs volunteer donor sourced domestic manufacturing.[7,8] In contrast to many countries, only 1% (2/213) of Finnish PWH tested positive for HIV antibodies between 1985 and 1989.[9] This is likely due to the self-sufficiency for the production of clotting factors of Finland and the low HIV prevalence in the Finnish population at the time. Even in Finland, however, 94% of severe haemophilia A patients older than 20 years and treated with local produced lyophilised concentrates from unpaid blood donations were anti-HCV positive in 1999,[10] demonstrating that in contrast to HIV, the pooling of large numbers of plasma donations resulted in high pool infectivity. In the Netherlands, 99% of those treated with non-viral inactivated large pool concentrates were anti-HCV positive, compared to 66% of those treated with cryoprecipitate.[11] A comparison between Scottish PWH who received locally produced factor concentrates and Danish PWH who received both local and American factor concentrates, reported HCV antibody prevalence of 16% and 59%, respectively.[12] In Sweden, where both American and Swedish factor concentrates were used, HIV-positive persons with haemophilia A received significantly more American concentrate.[13] Countries with poor access to concentrates have had low levels of viral infections in their PWH.

The pooling of donations was key to the infectivity of concentrates. Whereas pools produced from plasma donations usually included up to 10.000 donors, plasma obtained from whole blood donations could contain plasma from as many as 60.000 donors.[14] The

impact of the size of the plasma pool on final infectivity is debated. A modelling study from 1996 showed that the risk of exposure to infectious agents for patients requiring repeated treatments, such as PWH, would only have been minimally affected by large reductions in pool size.[14]

Another issue that reduced the prevalence of infections in persons with mild haemophilia A, was the use of desmopressin which induces the endogenous release of FVIII which can be sufficient for many treatments.[15]

The introduction of viral inactivation

The infection of many PWH with HIV led to the introduction of viral inactivation of concentrates in late 1983 and early 1984. The early virally inactivated concentrates were safe in terms of viral transmission when infused into chimpanzees, and although infectivity was reduced especially for HIV, some NANBH infections still occurred in PWH. The later viral inactivation procedures employing higher temperature, wet heat, pressure and chemicals were much more effective in eliminating hepatitis and HIV infectivity from concentrates.[16] Viral transmission was further reduced/eliminated due to the combination of viral inactivation and viral exclusion. Viral exclusion has been achieved through chromatographic and immunoaffinity protein purification techniques applied to high purity concentrates, and dedicated steps such as wet and dry heating, solvent/detergent treatment, and nanofiltration. Finally, procedures such as deferral of donors with risk factors for HIV infection as well as serological and nucleic acid amplification testing of pooled donations were introduced to reduce the risk of TTI. Although viral inactivation was highly effective against HIV and HCV, some PWH treated with FVIII in the early 1990s in Europe, USA and South Africa were infected with hepatitis A virus (HAV), a virus normally transmitted via the faeco-oral route.[17] The reason for this, turned out to be poor efficacy of the viral inactivation processes used at the time against lipid enveloped viruses such as HAV.[17] This resulted in the regulatory authorities recommending that all clotting factor concentrates should undergo two separate viral inactivation steps, a recommendation that is still in use today.[18]

Other concerns related to viral inactivation were the potential adverse effects of the inactivation steps. In particular, this concerned potential immunogenicity of inactivated products, resulting in alloantibodies against administered clotting factors. In Belgium and in the Netherlands, increased incidence of FVIII alloantibodies (inhibitors) was linked to the introduction of new FVIII products virally inactivated through pasteurisation.[19,20] Fortunately, inhibitors disappeared after switching product. Nonetheless, these occurrences served as a warning for the potential risks of adaptations in production or viral inactivation methods.

Potential infectivity of current plasma derived concentrates

Undoubtedly, the current plasma derived concentrates are the safest they have ever been. The possibility of infection with HIV and hepatitis C is theoretical as the measures instituted by manufacturers will not only prevent infected donors from donating, but the purification process in combination with viral inactivation processes are highly efficient in reducing and inactivating HIV and HCV.[16]

Transmission of other viruses remains possible on rare occasions. Parvovirus B19 causes a childhood illness called fifth disease and has been shown to be still transmissible by concentrates because none of the current viral inactivation steps can destroy it completely.[21] Another group of infective agents that cannot be destroyed by currently used viral inactivation procedures are prions such as classical and variant Creutzfeld Jacob Disease (vCJD). Although many patients with haemophilia have been exposed to plasma products made from donors who went on to develop vCJD, no patient with an inherited bleeding disorder has ever developed symptoms of vCJD. One person with haemophilia, however, who died from an unrelated cause and received treatment with plasma derived FVIII and non-leucodepleted red cells, was found to have prions in his spleen at autopsy.[22]

The natural history of hepatitis C virus infection in haemophilia

Studying the natural course of HCV infection is often limited by unknown dates of infection and inconsistent follow-up. However, for PWH the onset of the infection can be reasonably traced back to the first clotting factor concentrate infusion.[23] Furthermore, in many countries all PWH have been systematically tested for HCV infection, decreasing the risk of selection bias that occurs when patients are tested only once they develop symptoms or signs of chronic hepatitis. Finally, PWH are reviewed regularly at their haemophilia treatment centre, providing reliable follow-up data independent of HCV status. Therefore, PWH are a good population in which to study the natural history of HCV infection.

Acute HCV infection is asymptomatic in the majority of cases and therefore was rarely recognised in PWH during the HCV epidemic. The proportion of HCV-infected PWH in whom the infection did not progress to chronic HCV varies in different reports from 7% to 23%,[24–31] of which most estimates range between 10% and 20%.[24–28,31] These percentages of spontaneous clearance are slightly lower than the average 26% spontaneous clearance rate in other HCV populations.[32] Likely, this is due to the relatively high number of HIV co-infected PWH, which is known to significantly decrease the chance of spontaneous clearance.[24,33,34] In those in whom the HCV infection progressed to a chronic infection,

the most common HCV genotypes were genotype 1 (65-70%), followed by genotype 3 and 2 with 15-20% and 10-15%, respectively.[24–27,30,31]

Chronic HCV infection can lead to the development of liver fibrosis and eventually cirrhosis. The gold standard for diagnosis of liver fibrosis and cirrhosis is liver biopsy. The main study describing liver biopsy results in PWH is a series of 220 liver biopsies from a cohort of 781 HCV-positive PWH.[35] Advanced fibrosis or cirrhosis (Metavir fibrosis scores of ≥F3) was seen in 52 (24%), with a slightly higher mean fibrosis score in HIV-infected PWH.[35] It is known that HIV infection accelerates HCV-related liver fibrosis progression.[36] As liver biopsy is an invasive procedure with adherent risk of complications such as bleeding and therefore not routinely performed, potential confounding by indication is important to consider in interpreting these results.

More often than liver biopsy results, non-invasive liver stiffness measurements using transient elastography (TE) are reported as an indicator of liver fibrosis and cirrhosis in PWH (Table 1). In these studies, 40-50% of PWH had no or minimal fibrosis (F0-F1) after an infection duration of at least 20 years.[37–39] Severe fibrosis or cirrhosis (F3 or F4) was found in 30-35% of PWH.[37–40] These rates of progression to severe fibrosis and cirrhosis are comparable to those found in studies from the general population.[41,42] An important consideration when considering TE results, is that several factors can lead to false-positive elevated values, as explained below. Furthermore, selection bias is likely, as many HIV/HCV co-infected PWH already died because of opportunistic infections by the time TE became available.

Several studies describing the natural history of HCV-infected PWH have focussed on the occurrence of end-stage liver disease (ESLD) which in these studies is usually defined as the occurrence of decompensated cirrhosis, bleeding esophageal varices, hepatocellular carcinoma (HCC) or liver-related death. In three cohorts with at least 30 years of follow-up since HCV infection, the cumulative incidence of ESLD was between 10% and 15%.[24,28,29] The largest of these three cohorts was a multicentre study conducted by our group from the Netherlands and the UK, which included 863 HCV-seropositive patients with a median infection duration of 31 years.[24] Co-infection with HIV was present in 212 (25%) of patients, whereas co-infection with HBV was uncommon with only 16 Hepatitis B surface antigen (HBsAg) positive patients (2%). Of the 700 HCV-infected patients who developed chronic HCV, ESLD based on the criteria mentioned above occurred in 90 (13%) after a median infection duration of 23 years.[24] This rate was slightly higher in the group of 510 HCV patients without successful antiviral treatment, of whom 88 (17%) developed ESLD. The all-cause mortality at the end of follow-up was 28%, of which 28% was liver-related, being the second cause of death after HIV/AIDS (32%).[24] The

Table 1. Rates of progression of liver fibrosis in HCV-infected PWH as measured with transient elastography

Author, year	Patients	Age	Infection duration	F0-F1	F2	F3	F4
Patients with inherited bleeding disorders							
Posthouwer, 2006[37]	110 HCV mono-infected 11 HIV/HCV co-infected	Median 42 (range 16-86)	Median 34 (range 14–40)	48 (40%)	31 (25%)	22 (18%)	20 (17%)
Maor, 2019[38]	50 HCV-infected, 5 HCV cleared or cured. HIV-status not reported	40 ± 14	26 ± 5	25 (45%)	12 (22%)	10 (18%)	8 (15%)
Kitson, 2010[39]	41 HCV mono-infected 18 HCV/HIV co-infected	45 ± 2	16-35 years, not further specified	28 (48%)	12 (20%)	7 (12%)	12 (20%)
Vidovic, 2010[40]	63 HCV mono-infected 57 HCV/HIV co-infected 40 HCV cleared or cured 14 HIV-infected, HCV cleared or cured	Median 42 (range 22-83)	All >20 years, not further specified	**F0-F2** 123 (71%)		**F3-F4** 51 (29%)	
Reference studies from the general population							
Poynard, 2012[41]	1289 HCV mono-infected	49 (48-50)	Not reported	637 (49%)	395 (31%)		257 (20%)
Shili-Masmoudi, 2019[42]	1062 HIV/HCV co-infected	Median 46 (IQR 42–49)	Median 21 (IQR 16 - 25)	831 (78%)			231 (22%)

Data are reported as number (percentage) or mean ± standard deviation, unless otherwise noted. HCV: hepatitis C virus. PWH: people with haemophilia.

largest cohort in which progression of HCV infection to ESLD in PWH was evaluated, is an American and European collaboration of sixteen centres from 2002.[43] In this study, 1818 HCV-seropositive PWH were included with a relatively short follow-up of median 12 years. At the end of follow-up, 137 (8%) participants developed ESLD based on the criteria mentioned above, of which only two cases were HCC.[43]

An important risk factor for both progression of liver fibrosis and occurrence of ESLD in HCV-infected PWH is HIV co-infection. Although in recent years safer and less hepatotoxic antiretroviral therapy has resulted in a more similar progression of liver fibrosis in HIV/HCV co-infected patients,[44] virtually all co-infected PWH have been infected for at least thirty years, before these new treatment modalities became available. As a result, HIV co-infected PWH not only have higher fibrosis scores but also account for the majority of ESLD cases.[24,26,28,35,37,43] The large haemophilia cohort study from 2002 reported 127 ESLD cases in 1192 HIV-positive PWH compared to only 10 in 624 HIV-negative PWH.[43]

Cumulative incidences of ESLD at sixteen years follow-up were 14% and 3% for HIV-positive and negative HCV-infected PWH respectively. Likewise, in the cohort of 863 HCV-infected PWH with over 30 years of follow-up, ESLD rates were 22% and 7% in HIV-positive and negative HCV-infected individuals, respectively.[24] In this cohort, HIV co-infection was the strongest predictor of ESLD occurrence, with a hazard rate of 11.[24]

Besides HIV, several other factors are associated with progression of liver disease and occurrence of ESLD in HCV-positive PWH. The determinant most strongly associated with a decreased risk of developing ESLD is successful HCV antiviral treatment.[24,26–28,30] Nonetheless, despite successful treatment being a strong predictor of decreased ESLD risk, HCC and decompensated cirrhosis still occur after sustained virological response (SVR) or spontaneous clearance. This is infrequent and is predominantly seen in patients with liver cirrhosis before the start of HCV treatment or with other liver-related risk factors such as obesity and alcohol abuse.[24,28] Other factors associated with development of liver cirrhosis or ESLD are age at HCV infection,[24,26,28] age in general[30,31,43] and HBsAg positivity.[26,43]

The use of antiviral therapy for hepatitis C

The first clinical trial to treat NANBH in haemophilia with interferon (IFN) injections commenced two years before the discovery of HCV.[45] In the following decade, the addition of the oral antiviral drug ribavirin and later replacement of standard IFN with PEGylated IFN (PEG-IFN) improved the efficacy of HCV treatment. In 2006 we reviewed the publications on treatment of HCV in haemophilia and included 35 studies with 1151 PWH in the analysis.[46] In treatment-naive HIV-negative PWH, SVR rates were 22% for IFN monotherapy, 43% for IFN with ribavirin and 57% for PEG-IFN with ribavirin. In HIV/HCV co-infected PWH, SVR rates for IFN monotherapy were only 8%, whereas efficacy of IFN with ribavirin was comparable to HIV-negative PWH at 39%.[46] Subsequent studies evaluating PEG-IFN efficacy in HIV-positive PWH showed varying results, with SVR showing a range of 8% to 50% (Table 2).[47–52]

Treatment with PEG-IFN and ribavirin came at the cost of significant side-effects. Moreover, these regimens were less effective in HCV genotype 1 infections,[48] the most common genotype in HCV-infected PWH.[24] The introduction of direct-acting antivirals (DAA) drastically changed the landscape of HCV treatment. At first, so-called triple therapy became available, in which the protease inhibitors telaprevir or boceprevir were combined with PEG-IFN and ribavirin. These regimens showed high SVR rates of 60%-75% in treatment naïve patients with HCV genotype 1.[53] Apart from several case reports, no haemophilia-specific efficacy studies of these first-generation DAA were published. In 2016, Santagostino et al.[54] published a study in which 51 PWH were treated with a combination of Lambda-IFN, ribavirin and the second-generation DAA daclatasvir

Table 2. Overview of studies reporting HCV treatment efficacy in patients with inherited bleeding disorders

Author, year	Study design	Type of antivirals	HCV mono-infected (n)	SVR rate (n/n)	HIV/HCV co-infected (n)	SVR rate (n/n)
Posthouwer, 2006[46]	Review	IFN monotherapy	434	22% (95/434)	51	8% (4/51)
		IFN + rbv	407	41% (165/407)	23	39% (9/23)
		PEG-IFN + rbv	168	57% (96/168)	0	
Shire, 2006[47]	Prospective	PEG-IFN + rbv	11	45% (5/11)	11	27% (3/11)
Posthouwer, 2007 [48]	Retrospective	IFN monotherapy	101	29% (29/101)	35	20% (7/35)
		IFN + rbv	72	44% (32/72)	2	50% (1/2)
		PEG-IFN + rbv	62	63% (39/62)	23	48% (11/23)
Maor, 2008[49]	Retrospective	PEG-IFN + rbv	37	46% (17/37)	5	20% (1/5)
Katsarou, 2008[51]	Prospective	PEG-IFN + rbv	31	58% (18/31)	19	11% (2/19)
Denholm, 2009[50]	Retrospective	PEG-IFN + rbv	0		13	8% (1/13)
Alavian, 2010[116]	Prospective	PEG-IFN + rbv	367	61% (225/367)	0	
Moghaddam, 2012[117]	Prospective	PEG-IFN + rbv	45	96% (43/45)	0	
Honda, 2013[118]	Retrospective	PEG-IFN + rbv	23*	65% (15/23)	*	
Lin, 2014[119]	Prospective	PEG-IFN + rbv	12	67% (8/12)	0	
Yang, 2015[52]	Retrospective	PEG-IFN + rbv	102	86% (88/102)	2	50% (1/2)
Stedman, 2015[55]	Phase 2 trial	SOF/LDV + rbv	14	100% (14/14)	0	
Santagostino, 2016[54]	Phase 3 trial	Lambda-IFN + rbv + DAC	51	90% (46/51)	0	
Ackens, 2016[62]	Case report	SOF/DAC	0		2, with ESLD	100% (2/2)

Table 2. Overview of studies reporting HCV treatment efficacy in patients with inherited bleeding disorders (continued)

Author, year	Study design	Type of antivirals	HCV mono-infected (n)	SVR rate (n/n)	HIV/HCV co-infected (n)	SVR rate (n/n)
Walsh, 2017[57]	Phase 2 trial	SOF/LDV, SOF+rbv	94	98% (92/94)	26	100% (26/26)
Hezode, 2017[58]	Phase 3 trial	EBR/GZR	101	94% (95/101)	6	83% (5/6)
Lee, 2017[59]	Prospective	SOF/LDV, SOF+rbv or DCV/ASV	30*	93% (28/30)	*	
Uemura, 2017[56]	Prospective	SOF /LDV, SOF+rbv or SOF/DAC	0		27	100% (27/27)
Wiegand, 2017[63]	Retrospective	Various DAA regimens	18	94% (17/18)	0	
Mehta, 2017[64]	Retrospective	SOF/DCV	4	100% (4/4)	0	
Nagao, 2017[65]	Prospective	SOF/LDV	23	100% (23/23)	20	95% (18/20)
Xiao, 2019[120]	Retrospective	Various DAA regimens	0		12	100% (12/12)
Mancuso, 2020[61]	Prospective	Various DAA regimens	160	100% (160/160)	40	95% (38/40)
Guedes, 2020[67]	Retrospective	Various DAA regimens	16*	100% (16/16)	*	

*HIV status not reported. HCV: hepatitis C virus. SVR: Sustained Virological Response. IFN: Interferon. PEG-IFN: PEGylated Interferon. Rbv: ribavirin. SOF: sofosbuvir. LDV: ledipasvir. DAC: daclatasvir. ESLD: end-stage liver disease. EBR: elbasvir. GZR: grazoprevir. ASV: asunaprevir. VEL: velpatasvir. DAA: direct-acting antiviral.

(DAC), demonstrating 90% efficacy. However, despite its high efficacy this regimen was never widely used, because IFN-free, all-oral DAA regimens were introduced at around the same time. Current DAA can be divided in three classes, all targeting different parts of the viral genome responsible for replication. Besides the NS3-4A serine protease inhibitors (-previr), these are non-structural protein (NS)5A inhibitors (-asvir) and NS5B inhibitors (-buvir). Combinations of these classes of inhibitors result in SVR rates >95%, in general within 2-3 months of treatment.

Stedman et al.[55] were the first to publish IFN-free DAA results specifically for PWH. In their phase-2 trial published in 2015, all 14 PWH infected with HCV genotype 1 and treated with sofosbuvir (SOF)/ledipasvir (LDV) achieved SVR-12, defined as an undetectable viral load twelve weeks after cessation of HCV treatment. Subsequently, in 2017, results from four other DAA trials specifically for patients with inherited bleeding disorders were published (Table 2).[56–59] In a USA multicentre trial, SOF/LDV was administered to patients with genotype 1 or 4 and SOF plus ribavirin to patients with genotype 2 and 3.[57] SVR-12 rate in the 120 included patients was 98% (118/120), due to one relapse in a PWH with HCV genotype 3 infection and one patient being lost to follow-up. In another trial, elbasvir/grazoprevir was given to 47 patients with genotype 1 or 4 and either haemophilia or von Willebrand disease, resulting in a 89% (42/47) SVR-12 rate.[58] In Korea, 30 PWH were treated with different regimens, with a 93% SVR-12 rate due to two failures in genotype 1b patients receiving DAC/asunaprevir.[59] The final DAA trial in PWH was conducted in Japan, where 25 HCV/HIV co-infected PWH also receiving different regimens were all successfully treated.[56]

Besides these trials showing DAA to be highly effective in HCV-infected PWH, they also demonstrated that the drugs were generally well-tolerated and safe. Predominantly mild side-effects were reported in 60-90% of treated patients, being more frequent in those receiving ribavirin.[55–58] Most frequent side-effects were headache, fatigue and nausea, occurring in 10-30% of patients. Importantly, drug-related haemorrhage was very rare in these four trials, with only one patient having an episode of epistaxis that was considered drug-related.[57] An exception to this low rate of serious adverse events is seen in patients with decompensated Child-Pugh-B and C liver cirrhosis. After several reports of liver failure and death following treatment with DAA regimens containing a protease inhibitor (glecaprevir, grazoprevir, voxilaprevir) and a post-approval FDA safety warning,[60] these drugs should not be prescribed in patients with current Child-Pugh-B and C liver cirrhosis.

DAA efficacy has also been demonstrated in real-world reports of usage including PWH (Table 2). The largest study originates from Italy, in which 200 PWH were treated with different DAA regimens.[61] In this cohort, SVR-12 was achieved in 99% (193/195) of patients, while no DAA-related serious adverse events were seen. An SVR-12 rate

above 94% was also seen in all other published real-world studies (Table 1).[61–67] This high DAA treatment efficacy corresponds to efficacy rates seen in other HCV patients. Slightly lower SVR rates, although in general still above 90%, are seen in patients with genotype 3 infection or cirrhosis, while DAA treatment efficacy does not differ between HCV mono-infected and HIV/HCV co-infected patients.[68] The current state of the art DAA are glecaprevir with pibrentasvir and sofosbuvir with velpatasvir, generally prescribed for 8 and 12 weeks respectively. These great advances in HCV treatment have offered the perspective of HCV elimination within the haemophilia population, with Slovenia being the first country to actually report this milestone.[69]

The natural history of hepatitis B virus infection in haemophilia

The natural history of HBV is characterized by five different phases (Table 3).[70] HBsAg is detectable in the first four phases, which are mainly distinguished by the presence of hepatitis B e antigen (HBeAg) and whether there are increased transaminases as signs of hepatic inflammation.[70,71] Antiviral treatment should in general be considered in patients with prolonged HBeAg positive or negative hepatitis (as indicated by prolonged (>3 months) increased transaminases) and in those with signs of advanced fibrosis or cirrhosis. Current suppressive HBV treatment (entecavir, tenofovirdisoproxil and tenofoviralafenamide) is very effective and with only limited risk of side effects. Adequate HBV DNA suppression is eventually achieved by more than 95% of treated patients, thereby strongly reducing the incidence of cirrhosis, ESLD and HCC.[71] In absence of significant liver fibrosis, HBsAg positive PWH without current indication for antiviral treatment should be monitored with at least six monthly ALT measurements, and should be referred for consideration of antiviral treatment if ALT increases above the upper limit of normal.[70]

Table 3. Different phases of hepatitis B virus infection

	HBeAg positive*		HBeAg negative*		HBsAg negative
	Chronic infection	**Chronic hepatitis**	**Chronic infection**	**Chronic hepatitis**	
HBsAg	High	High/intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	$>10^7$ IU/ml	10^4-10^7 IU/ml	<2,000 IU/ml	>2,000 IU/ml	Usually undetectable
ALT	Normal	Elevated	Normal	Elevated#	Normal
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe	None

Table adapted from the EASL HBV guideline[70]. *Therapy should particularly be considered in patients with persistent HBeAg positive or negative hepatitis and in patients with cirrhosis. #Can be elevated persistently or intermittently. HBeAg: Hepatitis B e Antigen. HBsAg: Hepatitis B surface Antigen. HBV: Hepatitis B virus.

The fifth phase of HBV infection, most common in PWH, is the phase where serum HBsAg is negative and antibodies to hepatitis B core antigen (anti-HBc) and generally also HBsAg (anti-HBs) are positive.[70,71] Notably, patients who become HBsAg negative do not completely resolve their HBV infection, as they keep integrated covalently closed circular (ccc) HBV DNA in their hepatocytic DNA. Nonetheless, non-cirrhotic patients who achieve HBsAg seroconversion have a minimal risk of developing cirrhosis in absence of cofactors.[72] However, those who developed cirrhosis remain at significant risk for HCC. An important consideration for PWH ever infected with HBV, is the risk of HBV flare or reactivation during chemotherapy or immunosuppression. In these patients prophylactic antiviral therapy should be considered, depending on HBsAg status and severity of immune suppression.[70,73] During DAA therapy for HCV, HBsAg seroreversion should be monitored, although this occurs infrequently (1.4% of DAA-treated patients).[74]

Literature on the natural history of HBV in PWH is scarce. In recent studies aiming to find risk factors for ESLD, HBV infection was not considered, probably due to its low prevalence.[24,27] In 2002, data from a large combined American and European cohort were published, demonstrating a hazard rate for development of ESLD in HIV/HCV co-infected PWH of 8 for those with chronic HBV infection.[43] As discussed by the authors, an important note regarding these numbers is that only 9% of HIV/HCV co-infected PWH in the cohort were HBV unexposed, making the estimate of the impact of HBV infection imprecise. Furthermore, the study was published in a completely different antiviral treatment era. Nonetheless, virtually all PWH infected with these viruses were exposed before 1990, thus this study contains the most representative data on the natural history of HBV infection in PWH.[43]

In order to prevent HBV infection, all children and adults without (previous) HAV or HBV infection and likely to receive plasma derived concentrates should have be offered HAV and HBV vaccination. In PWH, subcutaneous administration is recommended above intramuscular administration, as it leads to comparable immunogenicity without the risk of intramuscular haematoma.[75,76]

Hepatitis delta virus (HDV) is a defective virus that requires the presence of hepatitis B surface antigens to replicate. Already in 1982, it was reported in Italy that HBsAg-positive PWH were at a high risk of HDV superinfection, with antibodies to delta virus found in 49% of HBsAg-positive adult PWH and 25% of HBsAg-positive children.[77] Conversely, in Germany anti-HDV was only found in 0.3% of HBsAg-positive blood donors, compared to 50% again in PWH.[78] HDV superinfection severely accelerates the rate of liver fibrosis progression, as already recognized in 1985 when HDV superinfection was found to be significantly more common in HBsAg-positive PWH with fulminant liver disease than without.[79] Due to the low prevalence of HBsAg in PWH nowadays, as well as the risk of liver-related mortality in those

infected with HDV long ago, current HDV prevalence in PWH is likely low, although definitive recent data are lacking. Recently a new promising antiviral agent, bulevirtide, which blocks the entry of HBV and HDB into hepatocytes, was conditionally approved by the EMA.[80]

Diagnosis, complications and therapeutical considerations in cirrhosis

Although it has been demonstrated that (especially transjugular) liver biopsy can be performed relatively safely in PWH,[81] staging of liver fibrosis is now usually determined with non-invasive methods for which no clotting factor correction is required. The most widely used laboratory-based tests in HCV patients are the AST to Platelet Ratio (APRI) and Fibrosis-4 Index for Liver Fibrosis (FIB-4).[82,83] Both tests require only regularly collected laboratory values and have demonstrated moderate to good accuracy. In a meta-analysis evaluating the accuracy of APRI in HCV patients, an APRI threshold of 1.0 had a 76% sensitivity, 72% specificity, 55% positive predictive value (PPV) and 69% negative predictive value (NPV) for predicting or excluding cirrhosis.[84] The accuracy of the FIB-4 index was evaluated in a series of 592 HCV-infected patients, showing a 74% sensitivity, 80% specificity and 95% NPV for excluding severe fibrosis (<F3) at a FIB-4 value <1.45 and a 38% sensitivity, 98% specificity and 82% PPV for predicting severe fibrosis (≥F3) at a FIB-4 value >3.25.[85]

The most frequently used method to assess liver fibrosis at present is transient elastography using FibroScan®. TE is valuable as it is cheap, fast, non-invasive and has excellent intra- and interobserver variability.[86] TE cut-off values for HCV patients are ≤7.0 kPa for F0-F1 (no or mild fibrosis); 7.1–9.4 kPa for F2 (moderate fibrosis); 9.5–12.4 kPa for F3 (advanced fibrosis); and ≥12.5 kPa for F4 (cirrhosis).[87] However, TE cannot accurately distinguish F0/1 from F2 or F3 from F4. At a cut-off value of 9.5, TE has 73-86% sensitivity, 85-91% specificity, 71-87% PPV and 81-93% NPV for the presence of advanced fibrosis or cirrhosis (F3/F4).[88,89] Importantly, several patient-related factors can result in false-positive elevated TE values, such as elevated transaminases, extra-hepatic cholestasis, right decompensation from cardiac or pulmonary causes and (more limited) non-fasting conditions.[90] Of particular relevance is that TE is quite unreliable in establishing fibrosis regression in HCV patients with previous F3/F4 fibrosis who have sustained viral response after successful antiviral therapy. Additional liver biopsy often shows persistent cirrhosis in patients with F0/1 or F2 fibrosis on TE.[91,92] Therefore, patients with radiologic evidence of advanced liver disease or F3/F4 fibrosis according to TE before antiviral therapy should in general remain in surveillance for HCC after SVR, even if TE suggests regression of fibrosis after the antiviral therapy.

Radiologic imaging is not very sensitive in diagnosis of advanced liver disease. Although ultrasound, CT-scan and MRI-scan can detect quite specific indications of advanced

cirrhosis such as liver nodularity or portal hypertension, their sensitivities and negative predictive values are low. Endoscopic surveillance for oesophageal varices is in general recommended in cirrhotic patients with a TE value ≥25 kPa and a platelet count <110 x 10^9 cells/L.[93] Nevertheless, current insights allow a more restrictive follow up of surveillance after successful anti HCV therapy in case of cirrhotic patients without or with small stable varices in absence of previous variceal bleeding or cofactors for progression of fibrosis.[73] Treatment of symptoms of cirrhosis is mainly limited to patients with signs of decompensated cirrhosis, such as hepatic encephalopathy, varices or ascites. Furthermore, as malnutrition and sarcopenia are frequent complications in patients with advanced liver disease, nutrition guidelines recommend dietary counselling, sufficient protein intake, late evening protein intake and especially in patients with ascites a maximum daily sodium intake of 80 mmol.[94]

Hepatocellular carcinoma

Liver cancer, in 90% of cases caused by HCC, is the fifth most prevalent and second most lethal type of cancer globally.[95] Among PWH the impact of HCC is even greater, as it is the most common type of cancer and both HCC incidence and mortality in PWH are greater than in the general population.[96,97] Furthermore, HCC incidence in PWH has been increasing in the last decades, as was demonstrated by a 3-fold increase in HCC prevalence between 1998 and 2014 in a large American analysis of hospital discharge data.[96] This increase was more pronounced, albeit not reaching statistical significance, from the 1.7-fold increase in non-haemophilic men during the same period.

An increase in HCC prevalence was also seen in the long-term follow-up study of 700 PWH with chronic HCV.[24] In this study, HCC was diagnosed in 22 (3%) of patients after a median infection duration of 29 years. Notably, nine (41%) of these cases occurred in the last six years of the follow-up, which lasted until 2012. HCC prevalence was even higher in similar but smaller cohorts from Ireland, Sweden and Scotland, with respectively 9%, 6% and 5% incidence after 30 years of HCV infection.[25,26,28] Most of these rates are higher than in the general HCV population, where the 30 years HCC risk is estimated to be between 1% and 3%.[98] In contrast to most reports, a large single-centre American study of 222 PWH with chronic HCV, reported only one (0.5%) HCC case after a median of 28 years of HCV infection.[29] Apart from treating the underlying viral hepatitis and advising to avoid alcohol and overweight, one could advise coffee consumption considering the negative association of (caffeinated or decaf) coffee (with dose-response relationship up to 3 cups) and prevalence of cirrhosis or HCC.[99] Furthermore, HMG reductase inhibitors (also known as statins) are associated with a lower risk of cirrhosis and HCC in patients with chronic liver disease.[100]

HCC surveillance is indicated for cirrhotic patients with an annual HCC incidence of 1.5% or greater.[101] Therefore, all PWH with cirrhosis should be offered HCC surveillance, unless HCC treatment would not be indicated due to severe comorbidity or not possible because of decompensated cirrhosis without perspective for future liver transplantation, as in decompensated cirrhosis palliative anti-tumour therapy or resection are in general contraindicated. Due to potential understaging with TE, the EASL also recommends surveillance in patients with chronic HCV infection and stage F3 fibrosis.[101] The goal of surveillance is detection of HCC at an early stage, as late-stage HCC has limited treatment options and poor survival. HCC surveillance is usually performed with 6-monthly ultrasound, with or without the biomarker alpha-fetoprotein (AFP). Importantly, liver inflammation can sometimes cause false-positive elevated AFP levels.[101]

Although successful HCV treatment strongly reduces the risk of HCC development,[102] patients with pre-treatment cirrhosis remain at risk.[103] In a large American non-haemophilic cohort, the annual HCC risks for cirrhotic patients after SVR were 3.7% and 1.2% for patients with pre-SVR FIB-4 scores above or below 3.25, respectively.[103] HCC incidence in pre-treatment non-cirrhotic patients was very low in this study. The recently published EASL HCV guideline recommends indefinite HCC surveillance for all successfully treated patients with Metavir F3 or F4 fibrosis scores.[68] As mentioned above, this should also be done when TE would suggest regression of fibrosis post-SVR.

Various treatment options exist for HCC, although curative treatment options are mainly limited to liver transplantation, resection and sometimes radiofrequent ablation (RFA). Survival is most favourable in the selected group of patients who are eligible for liver transplantation. Resection leads to a five-year survival of 60-80%.[101] Unfortunately, recurrence or de novo HCC are seen in 70% of patients after resection or RFA.[101,104] In case of advanced local growth or extrahepatic spread, palliative anti-tumour treatment options should be considered (e.g. percutaneous RFA/cryoablation, transarterial chemoembolization, selective internal radiation therapy and sorafenib.[101,104] There are few data on the impact and prognosis of these treatment strategies for PWH specifically, most of which are summarized in a review by Meijer et al.[104]

Liver transplantation in haemophilia

Orthotopic liver transplantation (OLT) is a definitive treatment option for patients with decompensated cirrhosis or early-stage HCC. The first liver transplant in a PWH was reported in 1985.[105] The transplanted liver is able to produce all clotting factors, usually at a sufficient level within 48-72 hours post-transplant.[106] As the concentration of produced clotting factors remains stable during long-term follow-up,[106] an important benefit of OLT in haemophilia is the functional cure of the bleeding disorder.

Several studies have compared OLT outcomes between PWH and non-haemophilic liver transplant recipients, although these are usually small and often lack long-term follow-up data. Despite perioperative clotting factor replacement, PWH undergoing OLT have been reported to have an increased risk of bleeding complications when compared to non-haemophiliacs.[107] However, this does not result in significant difference in in-hospital mortality between these groups.[107] Likewise, the post-transplant survival rates appears similar between PWH and non-haemophiliacs.[108,109] In various studies, the post-transplant survival rate for PWH after 1, 3 and 5 years range between 78-90%, 67-80% and 54-67%, respectively.[106,108–110] PWH undergoing OLT now are likely to have an improved survival rate compared to these historical cohorts. The most common cause of death after OLT in these studies was liver failure due to recurrent HCV or HCC,[24,106,108] for which many new treatment options have become available recently. In the general HCV population, this has already resulted in increased post-transplant survival in the DAA era.[111]

Liver disease in the upcoming era of new haemophilia therapies

Recent developments in haemophilia treatment have included gene therapy where the FVIII and FIX genes are inserted into the liver cells, enabling sustainable production of clotting factors after a single viral vector administration.[112] The most widely used method for gene replacement in rare genetic diseases employs Adeno-Associated Virus (AAV) as the vector. Although AAV has been considered to be a non-integrating vector, it rarely does integrate to a small degree. Importantly, when this low risk of integration is multiplied by the large number of infused AAV vectors and large number of hepatocytes, AAV integration is inevitable and occurs with an estimated frequency of 1 in 1,000 to 10,000 hepatocytes.[113] In theory, AAV integration next to an oncogene in a fibrotic or cirrhotic liver could lead to HCC development.

Recently, the discussion on whether this is an actual risk of AAV gene therapy has become very relevant after a participant of the UniQure AAV5-FVIII trial developed HCC one year after gene replacement therapy.[114] This participant had previously been successfully treated for HCV, had a prior HBV infection and was reported to have evidence of non-alcoholic fatty liver disease. At the time of writing, tumour histology and sequence results are still awaited. Ruling out involvement of AAV integration into the tumour DNA will be crucial for the future of AAV gene therapy.

As a number of other new non-replacement treatments are introduced for the treatment of haemophilia, clinicians should be alert to the facts that the new therapies could cause hepatic dysfunction or that a patient's damaged liver could impact the efficacy and safety of the therapy. We are not aware of any evidence to suggest that the bispecific

antibody, emicizumab, or the anti-TFPI therapies cause or are impacted by hepatic dysfunction. Pasi and colleagues[115] reported that 9 of 25 (36%) severe PWH treated with the siRNA molecule Fitusiran developed elevated alanine aminotransferase levels but these were transient with no chronic sequelae.

CONCLUSION

The introduction of viral inactivation of plasma derived concentrates, as well as the vaccination of patients against HAV and HBV and the increasing use of recombinant products has practically eliminated new hepatitis viral infections in haemophilia. For those already infected the use of DAA has made it possible to clear the hepatitis C virus from almost all the patients treated. Continued monitoring for HCC is required for individuals who already had cirrhosis at the time of clearance of the HCV.

Declaration of interest

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CHAPTER 3

LIVER-RELATED COMPLICATIONS BEFORE AND AFTER SUCCESSFUL TREATMENT OF CHRONIC HEPATITIS C VIRUS INFECTION IN PEOPLE WITH INHERITED BLEEDING DISORDERS

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ABSTRACT

Introduction

With availability of direct-acting antivirals (DAA), most persons with inherited bleeding disorders are currently cured of hepatitis C virus (HCV) infection. The risk of liver-related complications following HCV cure has not been reported for this population.

Aim

Reporting liver-related complications during long-term chronic HCV infection and following sustained virological response (SVR) in this population.

Methods

Retrospective follow-up of a prospective single-centre cohort of HCV antibody-positive persons with inherited bleeding disorders. Primary endpoint was liver-related complications (hepatocellular carcinoma (HCC), decompensated cirrhosis, bleeding gastroesophageal varices). Liver-related complications were reported separately during chronic HCV and following SVR, stratified for interferon-based and DAA-based SVR.

Results

In total 309/381 (81%) HCV antibody-positive individuals developed chronic HCV infection. Median follow-up was 44 years (IQR:34-50). Liver-related complications occurred in 36/309 (12%) of individuals with chronic HCV infection after median 31 years of chronic infection. Of 199 individuals with SVR, 97 were cured with interferon-based regimens and 102 with DAA after median infection durations of 29 and 45 years, respectively. At end of follow-up, respectively 21% and 42% had advanced fibrosis or cirrhosis. Post-SVR, seven (4%) individuals had a liver-related complication, mainly HCC (n=4). Incidence of liver-related complications per 100 patient-years post-SVR follow-up was 0.2 for interferon-cured and 1.0 for DAA-cured individuals (p=0.01).

Conclusion

Successful HCV treatment does not eliminate the risk of liver-related complications in persons with inherited bleeding disorders. Due to higher baseline risk, incidence was higher after DAA than interferon-based SVR. We advise continuing HCC surveillance post-SVR in all with advanced fibrosis or cirrhosis.

INTRODUCTION

Before 1992, nearly all persons with severe inherited bleeding disorders were infected with hepatitis C virus (HCV) through contaminated clotting factor products.[1] Among the 70-80% of HCV-infected individuals who developed chronic HCV infection,[1,2] liver-related morbidity has been one of the most frequent causes of death. In contrast to the general HCV population, the onset of HCV infection can be reasonably estimated among people with inherited bleeding disorders as most individuals were infected at their first infusion with clotting factor concentrates.[3]

Earlier studies from an international prospective cohort reported liver-related complications in 13% of persons with chronic HCV infection after median 23 years infection duration.[3,4] These data originate from the era of previously used and less effective interferon-based HCV therapy. Since then, treatment of HCV has improved greatly with the introduction of direct-acting antivirals (DAA) that achieve sustained virological response (SVR) in >95% of persons.[5]

Although successful HCV treatment is considered to substantially reduce the risk of liver-related complications, this risk is not entirely eradicated.[6,7] In the general HCV population, liver-related complications following SVR are more frequent after DAA-induced SVR than following interferon-induced SVR because in contrast to interferon, also patients with more advanced liver disease are eligible for DAA therapy.[6,8] To our knowledge, it has not been reported yet whether this applies to persons with inherited bleeding disorders. This issue is important to assess, as various HCV populations may differ markedly in prevalence of factors associated with unfavourable outcomes (e.g. human immunodeficiency virus (HIV) and hepatitis B virus (HBV) co-infections,[9] alcohol use, overweight[10] and socioeconomic status[11]). Furthermore, some authors argue that repeated exposure to HCV via frequent administration of contaminated clotting factor products has resulted in increased intra-individual HCV quasispecies diversity in this population, which could potentially influence disease course.[12,13] Finally, their almost universally long period of HCV infection makes them especially at risk for developing liver-related complications.

Nine years after the previous publication,[4] almost all participants in our cohort are currently successfully treated for their HCV infection. Our aims were to describe liver-related outcomes after median 35 years of chronic HCV infection and following successful HCV treatment in a large cohort of persons with inherited bleeding disorders. Additionally, we compared the incidence of liver-related complications between DAA-induced and interferon-induced SVR.

METHODS

Design and participants

This study was a retrospective follow-up of a prospective single-centre cohort conducted at the Van Creveldkliniek Haemophilia Treatment Centre (Department of Benign Haematology, University Medical Centre Utrecht, the Netherlands). This centre provides care for approximately 50% of the Dutch haemophilia population. The study cohort was set up in 2005 and consisted of all individuals with inherited bleeding disorders ≥18 years who ever tested HCV antibody-positive.[3] Data of HCV antibody-positive individuals who joined the haemophilia treatment centre after 2005 were added. All persons with inherited bleeding disorders treated with plasma-derived clotting factor products from large plasma pools were systematically screened for HCV infection since 1992.[1] Local haemophilia and liver-related guidelines are reported in the supplementary data. The study was approved by the medical ethics committee of the University Medical Centre Utrecht.

Data collection

We collected age, body mass index (BMI), haemophilia-related variables (type and severity of the bleeding disorder), alcohol use, HBV and HIV co-infections, and date and cause of death. HCV-related variables were date of infection, HCV RNA and genotype results, and HCV treatment history. Liver-related variables were abdominal ultrasound results, Fibroscan® (Echosens, Paris, France) measurements, liver-related laboratory results, results of endoscopy of the upper gastrointestinal tract and liver-related clinical complications.

Additional data for the current follow-up were collected until January 31, 2021. For individuals who moved to another haemophilia treatment centre since 2012, updated information on HCV status and occurrence of primary and secondary endpoints was requested from the other centre.

Outcomes and definitions

The primary endpoint was development of a first liver-related complication, defined as the occurrence of decompensated cirrhosis, bleeding gastroesophageal varices or HCC. Decompensated cirrhosis was defined as cirrhosis with ascites, clinically diagnosed hepatic encephalopathy, hepatorenal syndrome or jaundice. Secondary endpoints were occurrence of individual liver-related complications, liver-related mortality and overall survival.

As defined previously,[3,4] the date of first exposure to large pool clotting factor products or cryoprecipitate was assumed to be the date of HCV infection. For the individuals in whom this date was unknown, the median date of HCV infection from the cohort was imputed (i.e. January 1970). For individuals born after this date, the median age at first treatment for persons with severe haemophilia in our centre was imputed. Median age at first treatment in our centre was 1 year during the 1970s and 1980s.[14] Presence of advanced fibrosis or cirrhosis was defined as any Fibroscan® result ≥9.5 kPa, if diagnosed with radiologic imaging, or if there was a history of liver-related complications as defined above. Severity of cirrhosis was classified using the Child-Pugh score. Additional definitions are presented in the supplementary data.

Statistical analysis

Descriptive data were presented as numbers (percentages) or median (with interquartile range (IQR) or range). Characteristics were reported at the time of last clinical evaluation, regardless of HCV status, unless otherwise noted. Differences between groups were assessed for statistical significance using Fischer exact tests or Mann-Whitney U tests as appropriate.

Occurrence of liver-related complications was reported with 95% confidence interval for the entire cohort since HCV infection and for three subgroups: during chronic HCV infection, following spontaneous HCV clearance, and following successful HCV treatment. For the analysis of liver-related complications during chronic HCV infection or following spontaneous HCV clearance, progression to clinical endpoints was compared using Kaplan-Meier analysis. Follow-up started on the assumed date of HCV infection and ended at the moment of treatment-induced SVR, occurrence of the first liver-related complication, last clinical evaluation, or death, whichever came first. For the analysis of overall survival, follow-up ended at the last clinical evaluation or death, regardless of HCV status. Analysis of liver-related complications was stratified for HIV/HCV co-infected individuals, individuals with chronic HCV mono-infection and those with spontaneous HCV clearance. Regarding overall survival, the group with spontaneous HCV clearance was additionally stratified for HIV status. Kaplan-Meier curves were truncated if the number of persons at risk in a subgroup was below 10. To address the potential issue of competing risk of mortality and liver transplantation, the cumulative incidence function was calculated including mortality and liver transplantation as competing risks to liver-related complications in a sensitivity analysis.

To assess the association between overweight (BMI ≥25 kg/m^2) and liver-related complications during chronic HCV infection, Cox proportional hazards regression,

adjusted for severe alcohol use and HIV infection, was performed in individuals with ≥35 years of chronic HCV infection without liver-related complications.

Finally, liver-related complications following SVR were reported as incidence per 100 patient-years follow-up with 95% confidence interval. Follow-up for the post-SVR period started at cessation of the successful antiviral treatment and ended at the last clinical evaluation, liver-related complication or death, whichever came first. This analysis was stratified for treatment type, i.e. interferon-based SVR and DAA-based SVR. Differences in incidence rates between these treatment types were expressed as rate ratio (RR) with 95% confidence interval. Data were analysed using R (version 3.6.1, Vienna, Austria).

RESULTS

In total 382 persons were included (Table 1; 93% haemophilia A or B). Of these, 309 (81%) developed chronic HCV infection (Figure 1). HCV transmission occurred before 1991. Fifty-five (14%) individuals tested HIV antibody-positive, all infected before June 1985. Median follow up after HCV infection was 44 years (IQR 34 – 50, in total 15,784 patient-years). Median duration of chronic HCV infection was 35 years (IQR 27 – 43) and for those with successful antiviral therapy median follow-up post-SVR was six years (IQR 4 – 16).

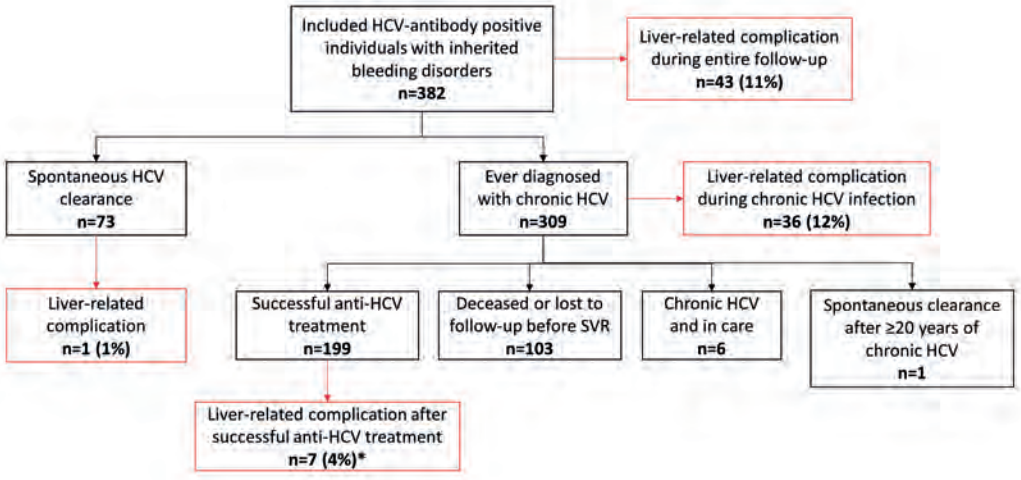

Figure 1. Flowchart
Liver-related complications were defined as the occurrence of decompensated cirrhosis, variceal bleeding or hepatocellular carcinoma. *One individual had a liver-related complication both during chronic HCV infection and after successful HCV treatment. Abbreviations: HCV: hepatitis C virus. SVR: sustained virological response.

Liver-related complications and overall survival since HCV infection

In the complete cohort, 43 (11%, 95%CI 8-15%) of the 382 HCV antibody-positive individuals developed a liver-related complication during the entire follow-up (Table 2). At the end of follow-up, 97 (25%, 95%CI 21-30%) individuals were deceased. Among the 309 individuals ever diagnosed with chronic HCV infection, liver-related death was the most common cause of death (n=23, 7%, 95%CI 5-11%; Table 2). Overall survival was comparable between HIV-negative persons with either chronic HCV infection or spontaneous HCV clearance (Figure 2). Between 1990 and 2000, 24 (50%, 95%CI 35-65%) individuals with HIV/HCV co-infection died, of whom 23 because of either acquired immune deficiency syndrome (AIDS, n=16) or liver-related complications (n=7).

Table 1. Characteristics of HCV antibody-positive persons with inherited bleeding disorders at their last clinical evaluation

	Spontaneous clearance	Ever diagnosed with chronic HCV
Number	**73**	**309**[†]
Total number of follow-up years	2944	12,839
Median follow-up (years)	41 (35 – 50)	44 (34 – 50)
Male sex	71 (97%)	297 (96%)
Diagnosis		
Haemophilia A	54 (74%)	250 (81%)
Haemophilia B	11 (15%)	42 (14%)
Von Willebrand disease	6 (8%)	8 (3%)
Other[‡]	2 (3%)	9 (3%)
Severe bleeding disorder	53 (73%)	234 (76%)
Age at HCV infection (years)	6 (1 - 22)	8 (2 - 18)
Age at end of follow-up (years)	51 (40 - 63)	52 (43 - 63)
HCV genotype		
1[§]		178 (58%)
2		29 (9%)
3		26 (8%)
4		7 (2%)
5		2 (1%)
Unknown	73 (100%)	67 (22%)
HIV infection	7 (10%)	48 (16%)
HBV infection		
HBsAg positive	4 (6%)	6 (2%)
HBsAg negative, anti-HBc positive	23 (32%)	122 (40%)
History of severe alcohol use[¶]	5 (7%)	37 (12%)
Body Mass Index (kg/m^2)	26 (24 - 28)	25 (22 - 27)
At least advanced fibrosis††	2 (3%)[f]	110 (36%)
Child-Pugh A/B/C	1/1/0	74/26/10
Alanine transaminase (IU/L)	22 (16 - 27)	28 (18 - 52)
Aspartate transaminase (IU/L)	24 (20 - 29)	26 (18 - 43)
Platelet count (*10^9/L)	236 (208 – 304)	215 (156 – 262)
Bilirubin (µmol/L)	10 (7 - 13)	11 (8 - 16)
Albumin (g/L)	42 (38 - 43)	42 (38 - 45)
International Normalized Ratio	1.0 (1.0 - 1.1)	1.0 (1.0 - 1.1)

Data are number (percentage) or median (interquartile range) unless otherwise noted. [†]One individual spontaneously cleared HCV after >20 years of chronic infection. [‡]Deficiency factor II (n=1), VII (n=1), X (n=4), XIII (n=2), or haemophilia carrier (n=2). [§]Subtypes: 1a n=53, 1a/b n=5, 1b n=74, 1c n=1, unknown n=45. [¶]Alcohol intake>20 units/week. [††]Fibroscan®≥9.5 kPa or radiological, histological or clinical diagnosis. [f]Both were diagnosed with alcoholic cirrhosis. Abbreviations: HCV: hepatitis C virus. HIV: human immunodeficiency virus. HBV: hepatitis B virus. HBsAg: hepatitis B surface Antigen. Anti-HBc: hepatitis B core antibodies.

Table 2. Liver-related complications and mortality after median 44 years since HCV infection in HCV antibody-positive persons with inherited bleeding disorders

	Complete cohort		Ever diagnosed with chronic HCV	
Number	**382**		**309**	
	Spontaneous clearance	**Ever diagnosed with chronic HCV**	**HIV/HCV**	**HCV mono**
Number	**73**	**309**	**48**	**261**
	Data are reported as number (percentage, 95% confidence interval)			
Liver-related complication	1[†] (1, 0-7)	42 (14, 10-18)	16 (33, 20-48)	26 (10, 7-14)
Decompensated cirrhosis	1 (1, 0-7)	31 (10, 7-14)	15 (31, 19-46)	16 (6, 4-10)
Hepatocellular carcinoma	1 (1, 0-7)	17 (6, 3-9)	2 (4, 1-14)	15 (6, 3-9)
Gastroesophageal bleeding	1 (1, 0-7)	10 (3, 2-6)	2 (4, 1-14)	8 (3, 1-6)
Liver transplantation	0	4 (1, 0-3)	0	4 (2, 0-4)
All-cause mortality	14 (19, 10-30)	83 (27, 22-32)	29 (60, 45-74)	54 (21, 16-26)
HIV/AIDS	2 (3, 0-10)	18 (6, 3-9)	18 (38, 24-53)	0
Liver-related	1[†] (1, 0-7)	23 (7, 5-11)	10 (21, 10-35)	13 (5, 3-8)
Non-variceal haemorrhage	1 (1, 0-7)	11 (4, 2-6)	0	11 (4, 2-7)
Malignancy[‡]	4 (5, 2-13)	7 (2, 1-5)	0	7 (3, 1-5)
Other	4 (5, 2-13)	16 (5, 3-8)	0	16 (6, 4-10)
Unknown	2 (3, 0-10)	8 (3, 3-8)	1 (2, 0-11)	7 (3, 1-5)

[†]Diagnosed with alcoholic cirrhosis. [‡]Malignancies not related to either HIV or HCV.
Abbreviations: HCV: hepatitis C virus. HIV: human immunodeficiency virus. AIDS: acquired immune deficiency syndrome.

Liver-related complications during chronic HCV infection

After median 31 years (range 16 – 49) of chronic HCV infection, 36/309 (12%, 95%CI 8-16%) individuals developed a liver-related complication. Main liver-related complications were ascites (n=21, 7%, 95%CI 4-10%), HCC (n=14, 5%, 95%CI 3-7%), variceal bleeding (n=8, 3%, 95%CI 1-5%) and hepatic encephalopathy (n=6, 2%, 95%CI 1-4%). Barcelona Clinic Liver Cancer (BCLC) stage at diagnosis of HCC was 0 (n=1), A (n=5), B (n=2), C (n=4), and D (n=2). Liver-related complications were more frequent in the HIV/HCV co-infected group (29% versus 8%, p<0.001), mainly because of higher incidence of decompensated cirrhosis (29% vs 5%, p<0.001). In HIV/HCV co-infected individuals, liver-related complications started after 20 years of HCV infection (Figure 3). After the introduction of more effective and less hepatotoxic HIV therapy in 1996, the incidence of liver-related complications decreased in HIV co-infected persons. In those diagnosed with chronic HCV mono-infection, liver-related complications started after 30 years of chronic HCV infection, with increasing incidence after 40 years.

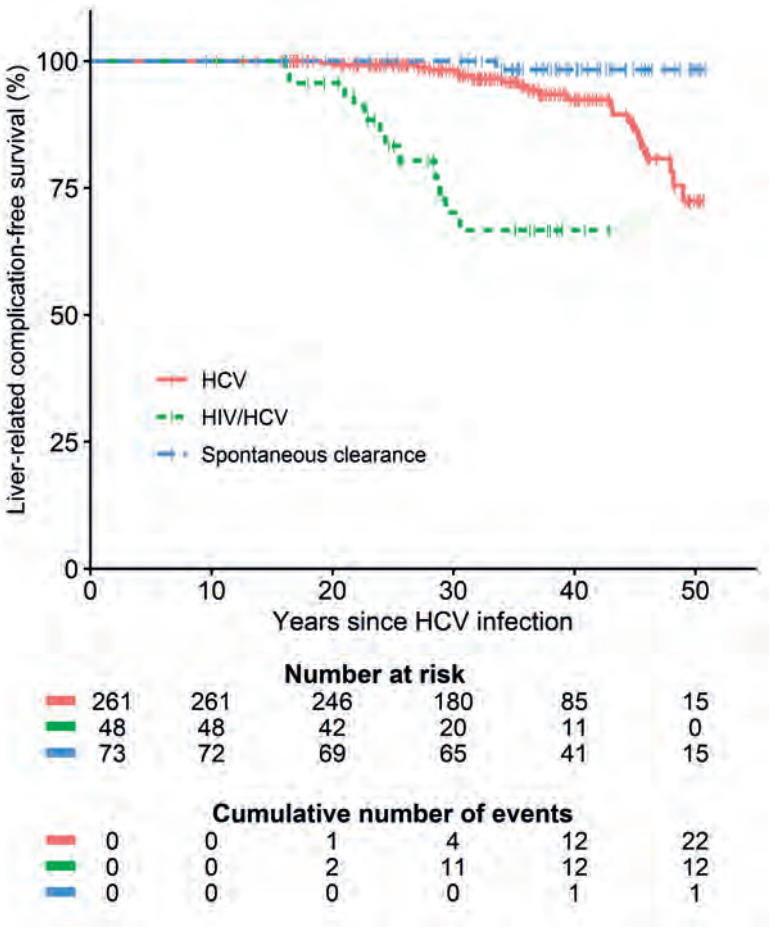

Figure 3. Liver-related complication-free survival stratified by infection status
Liver-related complications were defined as the occurrence of decompensated cirrhosis, variceal bleeding or hepatocellular carcinoma. Abbreviations: HCV: hepatitis C virus. HIV: human immunodeficiency virus.

In the sub-analysis including 150 individuals with ≥35 years of chronic HCV infection without prior liver-related complication, 16 individuals developed a liver-related complication during chronic HCV infection. No significant association was found between being overweight and the occurrence of liver-complications (adjusted HR 1.1, 95%CI 0.7-5.8, p=0.9). Among 226 individuals with chronic HCV who had an ultrasound examination, 46/226 (25%) had their most recent ultrasound examination indicating steatosis. Twelve (5%) of these individuals had a liver-related complication before achieving SVR, which was not associated with an ultrasound indicating steatosis (HR adjusted for HIV and severe alcohol use: 0.4, 95%CI 0.1-3.3, p=0.4).

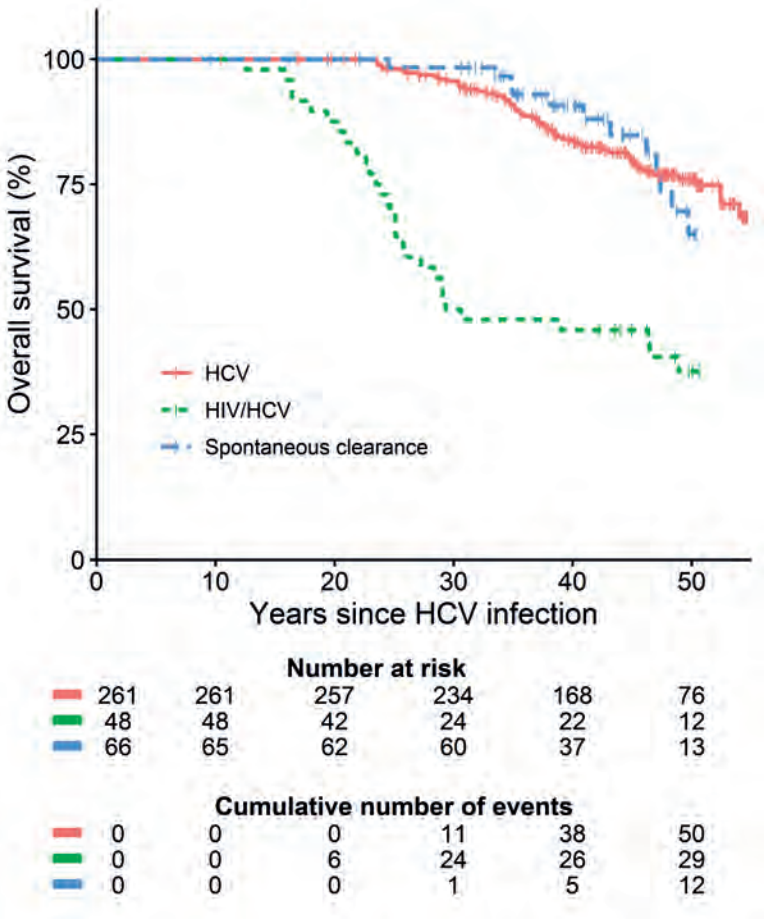

Figure 2. Overall survival stratified by infection status
HIV-positive individuals with spontaneous HCV clearance were excluded from this analysis as the number at risk in this subgroup was below 10 at start of follow-up (n=7). Abbreviations: HCV: hepatitis C virus. HIV: human immunodeficiency virus.

As there were no cases of liver transplantation prior to development of a liver-related complication, only mortality was included as competing risk in the sensitivity analysis (Supplementary figure 1). In this analysis, the incidence of liver-related complications was similar to the incidence in the regular survival analysis for all groups.

Antiviral therapy and SVR rates

Of the 309 persons diagnosed with chronic HCV infection, 223 (72%) were treated at least once with anti-HCV therapy. SVR percentages for first treatment with an interferon-based regimen were 40% (21/53) for interferon monotherapy, 43% (18/42) for interferon + ribavirin and 57% (55/97) for peg-interferon + ribavirin. SVR-rate was 68% (15/22)

for first- or second-generation DAA + peg-interferon + ribavirin and 96% (86/90) for interferon-free treatment based on second-generation DAA.

In total 199/223 (89%) of ever-treated individuals obtained SVR. Of the remaining individuals ever diagnosed with chronic HCV infection, 103 had either died (n=75) or were lost to follow-up before SVR (n=28), one individual spontaneously cleared the virus after 20 years of chronic HCV infection and six individuals remained chronically HCV-infected while in care in January 2021. At end of follow-up, 63/199 (32%) successfully treated individuals had at least advanced fibrosis. Laboratory parameters of liver function (serum bilirubin, PT, albumin values) did not change from pre-treatment to four years post-SVR in those with at least advanced fibrosis before start of HCV therapy (results not shown).

Liver-related complications following successful HCV treatment

Total follow-up after SVR was 1,626 patient-years (median 16, IQR 14-22) for the interferon-cured group (n=97) and 385 years (median 4, IQR 3-5) for the DAA-cured group (n=102). Infection duration was significantly longer among DAA-cured individuals (45 years versus 29 years, p<0.001; Table 3) and advanced fibrosis or cirrhosis at the end of follow-up was significantly more common in the DAA-cured group than in the interferon-cured group (42% versus 21%, p=0.001). Seven (4%, 95%CI 1.6-7.2) persons developed nine liver-related complications following SVR, of whom three individuals were interferon-cured and four DAA-cured (Table 4). These events were HCC (n=4), ascites (n=3) and variceal bleeding (n=2). BCLC stage of post-SVR HCC was A (n=2), C (n=1) and D (n=1). Median time between end of successful treatment and first liver-related event was 25 months (range 11-157). Only one of these individuals had a liver-related complication before SVR, with recurrent HCC following successful HCV treatment.

Incidence rates of liver-related complications following SVR were significantly higher in the DAA-cured group than in the interferon-cured group (RR 5.6, 95%CI 1.2-30.2, p=0.01). For individuals with at least advanced fibrosis, the difference between interferon and DAA was less pronounced with incidence rates of 1.0 and 2.2 per 100 patient-years in the interferon and DAA group, respectively (RR 2.2, 95%CI 0.5-11.9, p=0.28). Four persons were diagnosed with HCC post-SVR, of which three were *de novo* HCCs. HCC incidence rates per 100 patient-years post-SVR follow-up in persons with at least advanced fibrosis were 0.3 for the interferon-cured group and 1.6 for the DAA-cured group (RR 4.6, 95%CI 0.5-131.4, p=0.12). One individual with HCC following DAA-based HCV eradication had a liver-related death.

Table 3. Characteristics of successfully treated individuals, stratified for therapy type

	Interferon-cured	DAA-cured
Number	**97**	**102**
Age (median, IQR) (years)		
At start of treatment	37 (28 - 44)	49 (41 - 60)
At end of follow-up	54 (47 - 64)	52 (45 - 63)
HCV infection duration (years)	29 (23 - 34)	45 (38 - 48)
Advanced fibrosis or cirrhosis[†]	20 (21%)	43 (42%)
Child-Pugh A/B/C	18/2/0	42/1/0
HCV genotype		
1	36 (37%)	90 (88%)
2	21 (22%)	2 (2%)
3	17 (18%)	6 (6%)
4	1 (1%)	3 (3%)
5	1 (1%)	0
Unknown	21 (21%)	1 (1%)
HIV co-infection	9 (9%)	12 (12%)
No prior (Peg)-Interferon treatment	85 (88%)	61 (60%)
History of severe alcohol use[‡]	9 (9%)	10 (10%)
Body Mass Index (median, IQR) (kg/m²)	26 (23 – 28)	25 (22 – 28)
Platelet count (median, IQR)		
Prior to successful treatment	221 (181 – 271)	206 (165 – 254)
Two to four year post-SVR	234 (195 – 289)	228 (185 – 270)
APRI ≥1.0		
Prior to successful treatment	20/91 (22%)	27/102 (27%)
Two to four years post-SVR	3/80 (4%)	4/37 (11%)
FIB-4 ≥3.25		
Prior to successful treatment	2/91 (2%)	14/102 (14%)
Two to four years post-SVR	1/80 (1%)	4/37 (11%)

Data are reported as number (percentage) unless otherwise noted. Characteristics reported at the most recent clinical visit, unless otherwise noted. [†]Defined as a Fibroscan® result ≥9.5 kPa or radiological, histological or clinical diagnosis. [‡]Defined as an alcohol intake >20 units per week. Abbreviations: DAA: direct-acting antivirals. IQR: interquartile range. HCV: hepatitis C virus. HIV: human immunodeficiency virus. SVR: sustained virological response. APRI: AST to Platelet Ratio Index. FIB-4: Fibrosis-4 Score.

Table 4. Liver-related complications following successful HCV treatment

	Interferon-cured	DAA-cured
Number	**97**	**102**
Follow-up since SVR (in years)		
Median, IQR	16 (14 - 22)	4 (3 - 5)
Group total	1626	385
Liver-related complication after SVR[†]	3 (3%)	4 (4%)[b]
Per 100 patient-years	0.2 (95% CI 0.05 – 0.5)	1.0 (95% CI 0.3 – 2.5)
Per 100 patient-years (only F3/F4[§])	1.0 (95% CI 0.2 – 2.7)	2.2 (95% CI 0.7 – 5.2)
Hepatocellular carcinoma after SVR	1 (1%)	3 (3%)[‡]
Per 100 patient-years	0.1 (95% CI 0.003 – 0.3)	0.8 (95% CI 0.2 – 2.1)
Per 100 patient-years (only F3/F4[§])	0.3 (95% CI 0.02 – 1.6)	1.6 (95% CI 0.4 – 4.4)
Liver-related death after SVR	0	1 (1%)
Per 100 patient-years	0	0.3 (95% CI 0.01 – 1.3)
Per 100 patient-years (only F3/F4[§])	0	0.5 (95% CI 0.03 – 2.7)
All-cause mortality after SVR	4 (4%)	4 (4%)
Per 100 patient-years	0.2 (95% CI 0.8 – 5.9)	1.0 (95% CI 0.3 – 2.5)

Data are reported as number (percentage) or incidence (95% confidence interval) unless otherwise noted. [†]Defined as hepatocellular carcinoma, decompensated cirrhosis or variceal bleeding. [‡]One individual had a liver-related event prior to SVR (hepatocellular carcinoma), and a recurrent hepatocellular carcinoma following SVR. [§]Advanced fibrosis or cirrhosis. Defined as a Fibroscan® result ≥9.5 kPa or radiological, histological or clinical diagnosis.
Abbreviations: HCV: hepatitis C virus. DAA: direct-acting antivirals. SVR: sustained virological response. IQR: interquartile range. CI: confidence interval.

DISCUSSION

Following the introduction of highly effective DAA, virtually all persons with inherited bleeding disorders in our centre are now successfully treated for their HCV infection. Although successful HCV treatment substantially reduces the risk of liver-related complications, a residual risk remains. In our cohort, seven (4%, 95%CI 1.6-7.2) of the 199 successfully treated individuals had a liver-related complication during median six years post-SVR follow-up.

Our findings on the post-SVR clinical course of DAA-cured individuals with inherited bleeding disorders are in line with data from the European and American general HCV populations. This includes that the most frequent liver-related event following SVR in was HCC[15,16] and that post-SVR HCC incidence rates tended to be higher after DAA-based than interferon-based cure.[6,8] Importantly, studies with proper adjustment for differences in baseline characteristics demonstrate that SVR with DAA and interferon-based regimens result in similar HCC risk reduction.[6,8] Nonetheless, individuals treated with DAA have an inherently higher baseline HCC risk due to a higher prevalence of severe liver disease and longer infection duration. Hence, post-SVR HCC is expected to be more frequent in the DAA era.

The post-SVR HCC incidence of DAA-cured individuals with at least advanced fibrosis observed in our study was above the threshold for cost-effective post-SVR HCC surveillance of 1.3% per year reported by a recent analysis from Canada.[17] Validated prognostic tools to identify patients with cirrhosis having a sufficiently low risk to omit HCC surveillance are not yet available.[18,19] Furthermore, non-invasive tools for assessment of liver fibrosis are insufficiently accurate in detecting fibrosis regression following SVR.[18,20,21] Thus, in our opinion, continued bi-annual HCC surveillance with ultrasound ±alpha fetoprotein post-SVR for individuals with bleeding disorders and HCV-induced advanced fibrosis or cirrhosis is justified, in accordance with current HCV and HCC guidelines for the general HCV population.[19,22,23]

Being overweight after 35 years of chronic HCV infection was not significantly associated with increased occurrence of liver-related complications during chronic HCV infection. Although BMI is associated with hepatic steatosis in HCV-infected individuals,[24] there is inconsistency in literature regarding the association between being overweight and accelerated fibrosis progression in HCV patients.[10,25] A recent analysis of a large database on hospital inpatient discharge data in the USA indicated that non-alcoholic steatohepatitis (NASH) diagnosis based on ICD-10 codes was strongly associated with HCC among people with haemophilia.[26] For individuals without advanced fibrosis or

cirrhosis, additional HCC risk factors such as NASH, HBV infection and severe alcohol use can justify continuing liver fibrosis assessments following successful HCV treatment. Robust data on epidemiology and clinical outcomes of NASH in people with inherited bleeding disorders are still lacking, and are therefore an important topic for future research.

In the previous analysis of our cohort in 2012, the majority of included persons still had chronic HCV infection[4] and after a median duration of 33 years, 9% had developed a liver-related complication. For the current analysis, median HCV infection duration was extended to 35 years and complications during chronic HCV infection had increased to 12%. Although median infection duration was not extended much due to successful antiviral therapy, incidence of liver-related complications during chronic HCV infection had increased further. Since DAAs were allowed in the Netherlands for individuals with at least advanced fibrosis in November 2014, five patients were diagnosed with *de novo* HCC. In the seven years before DAA, seven cases were identified, indicating that prevalence did not decrease sharply following introduction of DAA. Physicians must therefore remain aware of the risk of liver-related complications, even after 35 years of complication-free chronic HCV infection and after SVR. Taken together, this underlines the importance of the arrival of DAAs and that HCV micro-elimination is paramount in this population with uniform long HCV infection duration.

To our knowledge, our study is the first to report data on incidence of liver-related complications following SVR in persons with inherited bleeding disorders. These data originate from a centre that provides care for a large part of the Dutch haemophilia population, with very long and consistent follow-up of individuals ever infected with HCV. Nonetheless, several limitations apply to our study. The survival curve of liver-related complications during chronic HCV infection might overestimate the incidence rate at the end of follow-up, as censoring due to successful treatment was not completely random because of patients with more advanced liver disease having a lower chance of achieving SVR with interferon-based treatment. Also, the exact date of HCV seroconversion was unknown since HCV testing was not available at the time of HCV transmission. As previously described,[3,4] the date of first exposure to large pool clotting factor products or cryoprecipitate was used, which was frequently followed by elevated transaminases indicating non-A, non-B hepatitis.[27,28]

Furthermore, our definition of at least advanced liver fibrosis if any Fibroscan® result was ≥9.5 kPa might have falsely classified some individuals as having at least advanced fibrosis, because several factors, such as inflammation and a non-fasting state, can lead to overestimation of fibrosis. Therefore, the incidence of post-SVR liver-related

complications in individuals definitively having at least advanced fibrosis will have been higher. In contrast, regression or normalization of Fibroscan® values post-SVR can be seen despite biopsy showing persistent cirrhosis.[20,21] Thus, we chose this definition to reduce the chance of missing individuals with at least advanced fibrosis post-SVR. Liver biopsies were not performed for staging of extent of fibrosis in in our cohort of people with inherited bleeding disorders, related to the assumed risk of post-procedural bleeding and early availability of Fibroscan® measurements. Furthermore, NASH data were not systematically collected, as controlled attenuation parameter measurements during Fibroscan® have only recently become available in our centre. Also, individuals who deceased before 1992 were not retrospectively tested for HCV antibodies. Therefore, some early mortality in HCV-infected persons from our centre might have been missed. However, this effect was likely small, as liver-related mortality was uncommon among people with haemophilia in these days.[29] Furthermore, post-SVR follow-up of DAA-cured individuals was still relatively limited, precluding definitive conclusions on liver-related complications during long-term post-DAA follow-up. Finally, in comparison to the previous follow-up studies,[3,4] the cohort in the current analysis was smaller as two centres from the UK (included in our previous report) were not able to participate in the current work due to Brexit and Covid-19 unforeseen circumstances. Due to the smaller cohort and the limited number of post-SVR liver-related complications, we were unable to reliably assess predictors of post-SVR liver-related complications.

CONCLUSION

Nearly all HCV-infected persons with inherited bleeding disorders in our centre have achieved HCV clearance. Nonetheless, our data show that a residual risk of liver-related complications remains following SVR. Presumably due to higher baseline risk, incidence of liver-related complications following DAA is higher than following interferon-based treatment. Therefore, we strongly advise continuing bi-annual HCC surveillance in all persons with advanced fibrosis or cirrhosis prior to successful DAA treatment.

DECLARATION OF INTEREST

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Supplementary material belonging to this chapter is available online.

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CHAPTER 4

HEPATITIS C VIRUS IN HAEMOPHILIA: HEALTH-RELATED QUALITY OF LIFE AFTER SUCCESSFUL TREATMENT IN THE SIXTH HAEMOPHILIA IN THE NETHERLANDS STUDY

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ABSTRACT

Introduction

Persons with hemophilia and hepatitis C virus (HCV) infection have a lower health-related quality of life (HRQoL) than those never HCV-infected. However, it is unknown whether HRQoL after HCV eradication is comparable to individuals never HCV-infected. We aimed to compare HRQoL between HCV-cured and never chronically HCV-infected persons with hemophilia.

Methods

All persons with hemophilia in the Netherlands were invited for a nationwide study conducted in 2018/2019. For the current analysis, participants born before 1992 with data on HRQoL and HCV status were included. HCV status was collected from medical records. HRQoL was measured by RAND-36 questionnaire, with a minimally important difference set at 4.0 points. Multivariable linear regression was used to adjust for age, hemophilia severity, HIV status and self-reported joint impairment.

Results

In total 486 persons were eligible; 180 were HCV-cured and 306 never chronically HCV-infected. Compared with those never HCV-infected, HCV-cured individuals were older (57 vs 53 years), more often had severe hemophilia (67% vs 21%) and reported more impaired joints (median 3 vs 0). Compared with those never HCV-infected, adjusted RAND-36 domain scores of HCV-cured individuals cured were lower on all RAND-36 domains except Pain, ranging from a difference of 4.5 (95%CI -8.8.- -0.3) for Physical functioning to 11.3 (95%CI -19.4 - -3.1) for Role limitations due to physical problems.

Conclusion

Despite effective HCV treatment, HRQoL of HCV-cured persons with hemophilia is still lower than HRQoL of those never chronically HCV-infected on all RAND-36 domains. This implies that careful psychosocial follow-up and support are indicated.

INTRODUCTION

Hemophilia is an inherited X-linked bleeding disorder characterized by bleeding tendency due to clotting factor VIII or IX deficiency. Health-related quality of life (HRQoL) of Dutch persons with hemophilia is lower than in the general Dutch population, with the exception of mental health[1]. HRQoL of persons with hemophilia is mainly dependent on severity of hemophilia, age, orthopedic status and co-morbidities[2,3]. One of the main co-morbidities in persons with hemophilia is HCV infection, which was widespread among persons with hemophilia as a result of receiving contaminated plasma-derived clotting factor concentrates before the 1990s[4].

HCV infection impacts HRQoL through fatigue, psychological effects (i.e. depression and cognitive impairment) and stigma[5]. In a cross-sectional study on HRQoL among persons with hemophilia in the Netherlands in 2001, chronic HCV infection was independently associated with a decreased score on the RAND-36 domains of General health and Energy/fatigue when compared with never HCV-infected persons with hemophilia[2]. Until 2014, HCV was treated with a combination of PEG-interferon and ribavirin, which was successful in less than 60% of cases and had many severe side effects, such as fatigue and depression[4,6]. In 2014, interferon-free direct-acting antiviral (DAA) therapy became available, with an effectivity over 95% and minimal side-effects[7]. This has made HCV elimination feasible[8]. Successful HCV treatment decreases long-term morbidity and all-cause mortality[9,10]. Additionally, studies in the general HCV mono-infected and HIV/HCV co-infected populations have shown that successful DAA treatment improves several domains of HRQoL[11,12].

For persons with hemophilia however, the effect of successful HCV treatment on HRQoL is insufficiently known. The only study on HRQoL of persons with hemophilia undergoing anti-HCV treatment reported decreasing RAND-36 domain scores during PEG-interferon treatment[6]. However, four weeks after cessation of treatment RAND-36 domain scores approached pre-treatment level, without any association between RAND-36 scores and virological response[6]. Persistent depression after cessation of therapy was also described[6]. It is unknown how HRQoL after HCV eradication compares to the HRQoL of those never chronically HCV-infected. Most HCV-cured persons with hemophilia had been infected for many decades, which might have left a physical, social and psychological impact. Identifying whether HRQoL remains affected after HCV eradication could aid tailored psychosocial support for those who need it. Therefore, we aimed to compare HRQoL between persons with hemophilia successfully treated for HCV and those never chronically infected.

METHODS

Design/Setting

The sixth Hemophilia in the Netherlands (HiN-6) study was the latest edition of a series of nationwide cross-sectional studies that assessed the medical, social and psychological status of persons with hemophilia in the Netherlands. All persons with hemophilia known at one of the hemophilia treatment centers were invited for participation. The study was approved by the medical ethics committee of the Leiden University Medical Center and all participants provided written informed consent for use of their data when required under Dutch law.

Data collection

All participants completed a survey between June 2018 and July 2019 that included questions on socio-demographic characteristics (age, education, income), functional outcomes (including HRQoL) and clinical characteristics (severity of hemophilia, bleeding episodes, orthopedic status, co-morbidities, use of clotting factor and other medication). Data on severity of hemophilia and co-morbidities (HCV status, HIV status, liver fibrosis, liver-related complications) were taken from electronic patient records using a standardized electronic case report form after the participant provided written informed consent for extraction of these data.

Selection criteria

All male adult and pediatric individuals with mild, moderate or severe congenital hemophilia A or B receiving hemophilia care in the Netherlands were eligible for inclusion in the HiN-6 study. Inclusion criteria for the current analysis were available HRQoL data and HCV data from the survey and medical files, respectively. Exclusion criteria were current HCV infection (i.e. last known HCV RNA result positive), ongoing antiviral therapy at the time of survey, and year of birth after 1991, as the risk of HCV infection through clotting factor replacement after 1991 was considered negligible.

Outcomes and definitions

Study outcomes were differences in RAND-36 HRQoL domain scores between persons with hemophilia with cured HCV and those never chronically HCV-infected. HCV status was categorized as either HCV-cured (i.e. ever HCV RNA positive, with an undetectable HCV RNA at least 24 weeks after cessation of interferon-based treatment or at least 12 weeks after cessation of DAA treatment), spontaneous HCV clearance (i.e. a positive HCV antibody or RNA result followed by a negative HCV RNA result in absence of a history of antiviral treatment), or never HCV-infected (i.e. negative HCV antibody status). Never chronically HCV-infected was defined as either never HCV-infected or spontaneous HCV

clearance. We hypothesized that in persons with hemophilia and spontaneous HCV clearance the physical and psychological impact of HCV infection on quality of life at present was very low, as spontaneous clearance usually occurs within 12 months[13], does not result in liver-related complications[14] and these individuals were only informed about their HCV antibody and RNA status after testing became available in 1990s[15], many years after the HCV transmission for the vast majority of the cohort.

HRQoL was assessed with the Dutch version of the RAND-36 questionnaire[16,17]. This questionnaire contains 36 items assessing the following eight domains: General health, Physical functioning, Energy/fatigue, Pain, Role limitations due to physical health problems, Role limitations due to emotional problems, Emotional well-being and Social functioning. Domain scores (ranging from 0-100) were calculated when at least half of the items of a domain had been completed, in accordance with RAND-36 scoring instructions. Participants were included if a score on at least one domain was available. Participants with a missing score on a domain were not considered for that specific analysis. The minimally important difference (MID), the threshold at which a difference in a domain score between groups was considered relevant, was set at 4 points for all RAND-36 domains[18,19].

Joint status was self-reported for the eight most commonly affected joints (i.e. left and right knees, elbows, ankles, and wrists), with scores reflecting functional limitation of 0 (no limitation), 1 (some limitation without daily problems), 2 (some limitation with daily problems) or 3 (severe limitation with complete loss of function). By summing up these joint scores a total joint limitation score ranging from 0 to 24 was calculated. Presence of advanced liver fibrosis or cirrhosis was noted if the most recent Fibroscan® result was ≥9.5 kPa or if there was a history of hepatocellular carcinoma, ascites, hepatic encephalopathy, bleeding esophageal varices or liver transplantation. Within the HCV-cured group, a subgroup was defined as individuals with sequelae of the cured HCV infection, defined as either the presence of advanced liver fibrosis or cirrhosis, self-reported residual symptoms of the HCV infection, or self-reported ongoing side-effects of previous antiviral therapy. HCV treatment was categorized as interferon-containing regimens (including regimens combining PEG-interferon and DAA) and interferon-free DAA regimens. Education status was reported as highest level of education according to the International Standard Classification of Education (ISCED) that was successfully completed.

Statistical analysis

Descriptive data are presented as numbers (percentages), mean ± standard deviation (SD) or median (interquartile range (IQR)), depending on variable type and distribution. Multivariable linear regression was performed to assess the association of a cured HCV status versus never chronically HCV-infected on each of the eight RAND-36 domains and to

adjust the RAND-36 domain score differences for potential confounding factors. Variables included as covariates were severity of hemophilia (categorized as mild (Factor VIII/IX activity 0.05-0.4 IU/mL), moderate (Factor VIII/IX activity 0.01-0.05 IU/mL) or severe (Factor VIII/IX activity <0.01 IU/mL)), age, self-reported joint impairment score and HIV status. In a sensitivity analysis the use of prophylaxis was added as an additional covariate.

The main analysis included all participants either HCV-cured or never chronically HCV-infected. Furthermore, we conducted four sub-analyses. First, to explore whether RAND-36 score differences were due to HCV infection sequelae, we compared RAND-36 domain scores between individuals never chronically HCV-infected and cured persons with hemophilia excluding the subgroup of HCV-cured individuals with HCV infection sequelae. Second, for a more comparable control group regarding age and hemophilia severity, a sub-analysis was conducted comparing HCV-cured persons with hemophilia and those with spontaneous HCV clearance. Third, we compared RAND-36 domain scores between HCV-cured participants and the never HCV-infected participants without those with spontaneous HCV clearance, thus only including successfully treated and HCV antibody-negative participants. Fourth, to assess the effect of prior interferon treatment on HRQoL, within the HCV-cured group RAND-36 domain scores were compared between those who ever had interferon-containing treatment to those who only received interferon-free DAA regimens. This third sub-analysis included a sensitivity analysis with the presence of advanced liver fibrosis or cirrhosis as an additional covariate. Additionally, effect of time since successful treatment on RAND-36 domain scores was analyzed as a continuous variable within the HCV-cured group using univariable linear regression. Data were analyzed using R (version 3.6.1, Vienna, Austria).

RESULTS

Participant characteristics

Invitations for the HiN-6 study were sent to 1746 adult persons with hemophilia known at one of the eight Dutch hemophilia treatment centres (Figure 1). Fully or partially completed surveys were returned by 808 participants (response 46%). After excluding individuals who were born ≥1992 (n=122), who did not provide written informed consent for additional data collection from their medical records (n=155), with ongoing HCV infection (n=7), with an unclear HCV status (n=2), with ongoing DAA therapy (n=1), without scores on any of the RAND-36 domains (n=31), or with successful treatment in between the date of returning the survey and the date of data collection from electronic patient record (n=4), 180 HCV-cured persons and 306 never chronically HCV-infected persons were included in the current analysis. The group never chronically HCV-infected included 43 individuals who had spontaneously cleared HCV.

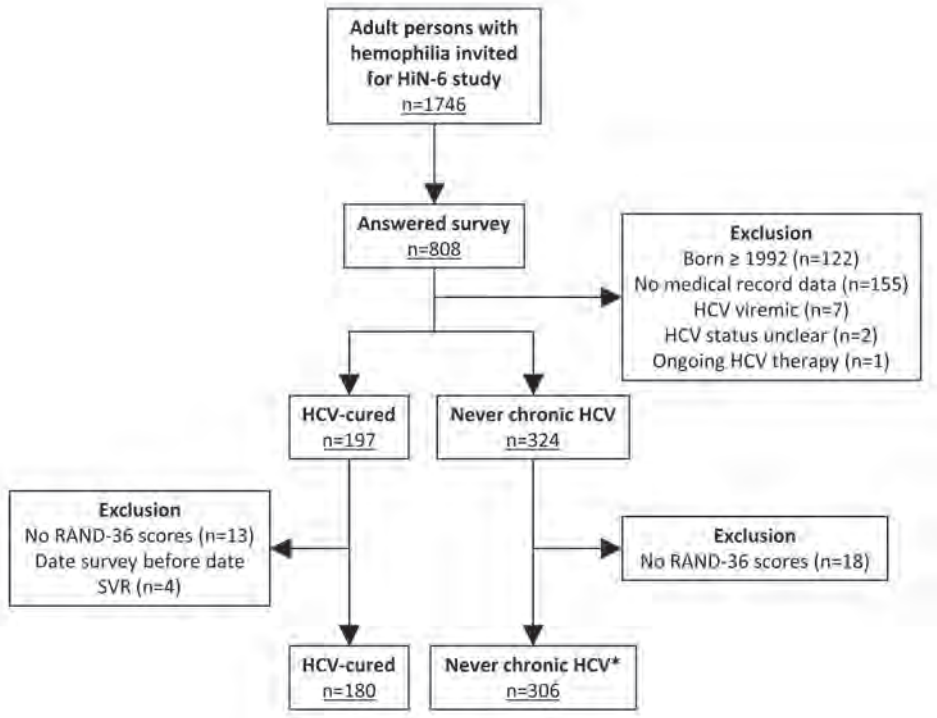

Figure 1. Flowchart of participant selection from the sixth Hemophilia in the Netherlands study (HiN-6) HiN: Hemophilia in the Netherlands. HCV: Hepatitis C Virus. *Including 43 participants with spontaneous clearance of HCV.

Table 1. Characteristics of included persons with hemophilia

	Never chronic HCV (n=306)	HCV-cured (n=180)
Age (median, IQR)	53 (38 - 64)	57 (47 - 63)
Hemophilia A	282 (92%)	149 (83%)
Severity of hemophilia		
Mild	185 (60%)	35 (19%)
Moderate	57 (19%)	25 (14%)
Severe	64 (21%)	120 (67%)
Current use of prophylaxis	65 (21%)	107 (59%)
Joint bleeding in the past 12 months	59 (19%)	91 (51%)
Other bleeding in the past 12 months	94 (31%)	81 (45%)
Self-reported joint impairment score (median, IQR)	0 (0 - 2)	7 (1 - 13)
Alcohol use >20 units weekly (self-reported)	12 (4%)	6 (3%)
HIV infection	3 (1%)	15 (8%)
Advanced liver fibrosis or cirrhosis*	0	25 (14%)
HCV treatment history		
(PEG)-IFN ± ribavirin	n.a.	135 (75%)
PEG-IFN + DAA + ribavirin	n.a.	11 (6%)
DAA ± ribavirin	n.a.	70 (39%)
Years since SVR (median, IQR)	n.a.	9 (3 - 15)
SVR more than 5 years ago	n.a.	102 (57%)
Employment		
Currently employed / Studying	210 (69%)	94 (52%)
Unemployed	5 (2%)	6 (3%)
Retired	57 (19%)	37 (21%)
Occupational disability	12 (4%)	28 (16%)
Missing / prefer not to say	22 (7%)	15 (8%)
Highest level of education completed		
Primary or lower secondary (ISCED 1/2)	79 (26%)	54 (30%)
Higher secondary (ISCED 3)	95 (31%)	56 (31%)
Bachelor/Master or equivalent (ISCED 6/7)	118 (39%)	65 (36%)
Missing / prefer not to say	14 (5%)	5 (3%)

*Fibroscan® value of ≥9.5 kPa or history of liver transplantation, hepatocellular carcinoma or decompensated cirrhosis.
Abbreviations: HCV: hepatitis C virus. IQR: interquartile range. (PEG)-IFN: (Pegylated)-Interferon. DAA: Direct-acting antivirals. n.a.: not applicable. SVR: Sustained Virological Response. ISCED: International Standard Classification of Education.

Compared with never chronically infected persons with hemophilia, cured participants more frequently had severe hemophilia (67% versus 21%; Table 1), were older (median 57 versus 53 years), reported more impaired joints (median number of 3 impaired joints, IQR 1 – 6, versus 0, IQR 0 – 2; median joint impairment score 7, IQR 2-13, versus 0, IQR 0-2), more often had an occupational disability (16% versus 4%) and more often had HIV infection (8% versus 1%). Of the 18 included HIV-positive individuals, 17 had an undetectable HIV viral load, whereas one person was not receiving antiretroviral therapy and had a detectable HIV viral load. In the successfully HCV treated group, 56% was cured with (PEG)-interferon with or without ribavirin between 1994 and 2013, 5% with an interferon-containing DAA regimen between 2012 and 2014, and 39% with interferon-free DAA between 2012 and 2018. Median number of years since successful HCV treatment was 15 (IQR 12 - 18), 5 (IQR 5 - 5) and 2 (IQR 2 - 3) for persons cured with (PEG)-interferon ± ribavirin, an interferon-containing DAA regimen or interferon-free DAA, respectively.

Health-related quality of life

HCV-cured and never chronically HCV-infected persons with hemophilia

HCV-cured persons with hemophilia had lower scores on all eight RAND-36 domains compared with those never chronically HCV-infected (Figure 2). After adjustment for age, severity of hemophilia, self-reported joint impairment score and HIV status, a decrease in this difference was seen for all domains except emotional well-being and role limitations due to emotional problems. Nonetheless, scores remained lower on all RAND-36 domains,

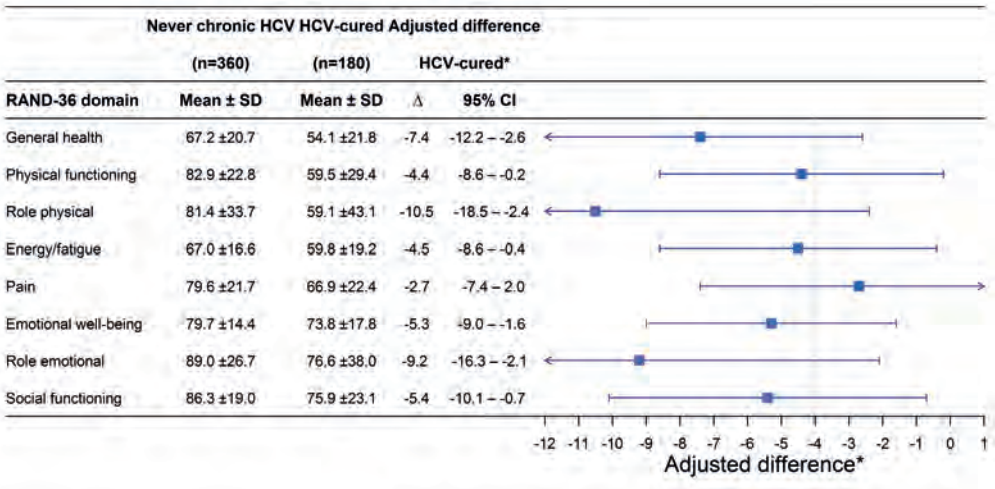

Figure 2. Differences in RAND-36 domain scores between HCV-cured persons with hemophilia and persons with hemophilia never chronically HCV-infected

The minimally important difference was set at 4 points for all RAND-36 domains. *****Adjusted for age, HIV, joint status and hemophilia severity. HCV: hepatitis C virus. SD: standard deviation. CI: confidence interval.

with the difference exceeding the MID threshold of 4 points on all domains except for Pain. Largest differences were seen in the domains General health, Role limitations due to physical problems and Role limitations due to emotional problems. The addition of prophylaxis as an additional confounder did not change the adjusted differences (data not shown).

Individuals with and without HCV infection sequelae

In total, 41 cured individuals had sequelae of the previous HCV infection, such as advanced liver fibrosis or cirrhosis, self-reported residual symptoms or self-reported ongoing side-effects of antiviral treatment. These 41 persons had lower scores on all eight RAND-36 domains than the other 139 HCV-cured individuals who did not have sequelae (Table 2). The 139 participants without HCV infection sequelae still had clinically relevant differences for the domains General health, Role limitations due to physical problems and Role limitations due to emotional problems compared with never chronically infected individuals (Table 3).

Persons with hemophilia either HCV-cured or with spontaneous HCV clearance

In the second sub-analysis, RAND-36 domain scores were compared between the 43 persons with spontaneous HCV clearance and 180 HCV-cured individuals. Participants with spontaneous HCV clearance had a median age of 56 years (IQR 42 – 67; Supplementary Table 1), 51% had severe hemophilia and median joint impairment score was 5 (IQR 0 – 10). Mean RAND-36 scores of individuals with spontaneous HCV clearance were higher than scores of successfully treated persons, with adjusted differences exceeding the MID threshold on all domains except Pain and Emotional well-being (Figure 3).

Persons with hemophilia either HCV-cured or never HCV-infected

In the third sub-analysis, participants with spontaneous HCV clearance were excluded from the never chronically HCV-infected group. The remaining group of HCV antibody-negative persons had mainly mild or moderate hemophilia (84%; Supplementary Table 2), with a median self-reported joint impairment score of 0 (0 – 1). Adjusted RAND-36 domain scores were in favor of the HCV antibody-negative group on all eight domains (Supplementary Table 3).

Impact of interferon-containing treatment on HRQoL

In the fourth sub-analysis, within the HCV-cured group RAND-36 domain scores were compared between those who ever received (PEG)-interferon (n=135) and those only treated with interferon-free DAA (n=44), while one HCV-cured individual was excluded from this analysis as treatment type was unknown. After adjustment for age, HIV and joint status and hemophilia severity the only difference was found in the domain Energy/fatigue, with a difference of 4.7 points in favor of those ever treated with interferon (Table 4). Advanced liver fibrosis or cirrhosis was reported in 23% of the DAA group versus 11%

Table 2. Characteristics and mean RAND-36 domain scores of cured persons with hemophilia, stratified for presence of sequelae of the cured HCV infection*

	Persons with hemophilia without sequelae (n=139)	Persons with hemophilia with sequelae* (n=41)
Characteristics		
Age (median, IQR)	55 (46 - 63)	58 (52 - 65)
Severe hemophilia	95 (68%)	25 (61%)
Joint impairment score (median, IQR)	6 (2 - 13)	11 (0 - 13)
HIV infection	8 (6%)	7 (17%)
Advanced fibrosis or cirrhosis	0	25 (61%)
Employment		
Currently employed / Studying	79 (57%)	15 (37%)
Unemployed	5 (4%)	1 (2%)
Retired	26 (19%)	11 (27%)
Occupational disability	17 (12%)	11 (27%)
Missing/prefer not to say	12 (9%)	3 (7%)
RAND-36 domain scores (mean + SD)		
General health	57±21	45±23
Physical functioning	62±29	51±30
Role physical	64±42	43±43
Energy/fatigue	62±18	54±21
Pain	69±22	61±24
Emotional well-being	75±17	69±20
Role emotional	78±38	73±38
Social functioning	79±22	67±25

*Sequelae of the cured HCV infection were defined as either the presence of advanced liver fibrosis or cirrhosis, self-reported residual symptoms of the HCV infection, or continuing self-reported ongoing side-effects of previous antiviral therapy.
Abbreviations: HCV: hepatitis C virus. IQR: interquartile range. SD: standard deviation.

of the interferon-experienced group. Additional adjustment for the presence of advanced liver fibrosis or cirrhosis in this sub-analysis did not affect differences in domain scores between groups. The effect of time since successful treatment on RAND-36 domain scores was limited, with change in domain score per year since successful treatment ranging between -0.1 and 0.2 (data not shown).

Table 3. Differences in RAND-36 domain scores between HCV-cured persons with hemophilia and persons with hemophilia never chronically HCV-infected, stratified for presence or absence of sequelae of the cured HCV infection*

	Adjusted difference HCV-cured compared with never chronically infected participants^ (n=180 vs n=306)		Adjusted difference excluding participants with sequelae of the cured HCV infection*^ (n=139 vs n=306)	
RAND-36 domain	**Δ**	**95% CI**	**Δ**	**95% CI**
General health	-7.6	-12.3 - -2.9	-4.5	-9.5 - 0.6
Physical functioning	-4.5	-8.8 - -0.3	-2.0	-6.3 - 2.5
Role physical	-11.3	-19.4 - -3.1	-5.9	-14.3 - 2.6
Energy/fatigue	-5.1	-9.2 - -1.0	-3.2	-7.5 - 1.2
Pain	-3.1	-7.8 - 1.5	-0.8	-5.7 - 4.1
Emotional well-being	-5.4	-9.0 - -1.7	-3.5	-7.4 - 0.3
Role emotional	-9.9	-17.1 - -2.7	-8.6	-16.2 - -0.9
Social functioning	-6.1	-10.8 - -1.4	-3.6	-8.5 - 1.3

*Sequelae of the cured HCV infection were defined as either the presence of advanced liver fibrosis or cirrhosis, self-reported residual symptoms of the HCV infection, or continuing self-reported ongoing side-effects of previous antiviral therapy. ^Adjusted for age, HIV status, joint score and severity of hemophilia. Minimally important difference was established at a difference of 4 points.
Abbreviations: HCV: hepatitis C virus. SD: standard deviation. CI: confidence interval.

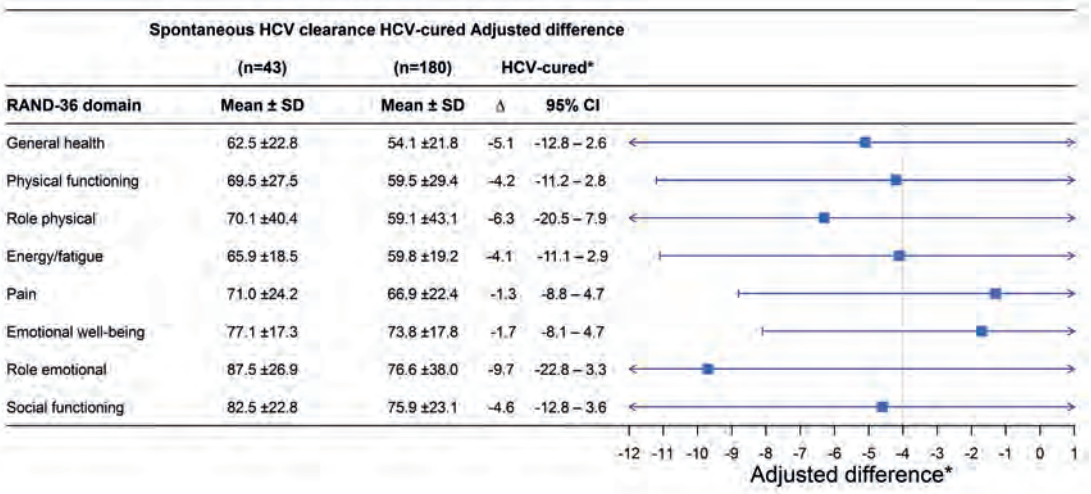

Figure 3. Differences in RAND-36 scores between HCV-cured persons with hemophilia and persons with hemophilia with spontaneous HCV clearance
The minimally important difference was set at 4 points for all RAND-36 domains. *****Adjusted for age, HIV, joint status and hemophilia severity. HCV: hepatitis C virus. SD: standard deviation. CI: confidence interval.

Table 4. Differences in RAND-36 scores between HCV-cured persons with hemophilia with or without interferon treatment experience

	Only DAA treatment (n=44)	(PEG)-Interferon experienced (n=135)*	Difference (PEG)-Interferon experienced adjusted^		Sensitivity analysis, additional adjustment for presence of advanced fibrosis/cirrhosis	
RAND-36 domain	**mean ±SD**	**mean ±SD**	**Δ**	**95% CI**	**Δ**	**95% CI**
General health	52.2 ±23.8	54.5 ±21.2	1.0	-7.0 - 8.9	0.4	-7.6 - 8.4
Physical functioning	53.6 ±29.8	61.5 ±29.2	1.2	-6.6 - 9.1	0.1	-7.9 - 8.0
Role physical	55.5 ±43.8	60.7 ±42.7	-0.5	-15.8 - 14.9	-0.5	-16.1 - 15.0
Energy/fatigue	56.8 ±20.5	60.9 ±18.8	4.2	-3.1 - 11.5	4.1	-3.2 - 11.5
Pain	64.0 ±24.0	68.0 ±21.9	2.2	-5.5 - 9.9	2.5	-5.3 - 10.2
Emotional well-being	72.4 ±19.9	74.2 ±17.2	2.8	-3.8 - 9.4	2.8	-3.9 - 9.4
Role emotional	74.8 ±40.0	77.2 ±37.6	1.9	-12.5 - 16.4	1.8	-12.8 - 16.5
Social functioning	73.5 ±27.6	76.9 ±21.4	2.5	-6.1 - 11.0	2.2	-6.5 - 10.8

Treatment type was unknown in one of the HCV-cured persons with hemophilia. *Including those treated with PEG-Interferon + Boceprevir/Telaprevir and those cured with interferon-free DAA after prior unsuccessful interferon-containing treatment. ^Adjusted for age, HIV status, joint score and severity of hemophilia. Minimally important difference was established at a difference of 4 points.
Abbreviations: HCV: hepatitis C virus. SD: standard deviation. CI: confidence interval. DAA: direct-acting antivirals.

DISCUSSION

The vast majority of HCV-infected persons with hemophilia in the Netherlands has been successfully treated with anti-HCV therapy. Results from our nationwide study demonstrate that despite HCV eradication, previously HCV-infected persons report lower RAND-36 domain scores than individuals never chronically HCV-infected. Domain scores remain lower after adjustment for confounders, for all domains except for Pain. Also after excluding those with HCV-related sequelae, differences remained on the domains General health, Role limitations due to physical problems and Role limitations due to emotional problems. These results imply that for some persons with hemophilia residual effects of the decades-long chronic HCV infection continue to affect multiple domains of their HRQoL.

There are several possible explanations for our findings. The subgroup of 41 participants with HCV infection sequelae had lower scores on all eight RAND-36 domains compared with the other 139 HCV-cured individuals. This indicates that in persons with hemophilia with advanced fibrosis and cirrhosis or with ongoing symptoms, the previous HCV infection has the largest residual impact on HRQoL. Nevertheless, also after exclusion of this group, differences still remained for the RAND-36 domains General health, Role limitations due to physical problems and Role limitations due to emotional problems. Indeed, literature from the general population suggests that also chronically HCV-infected individuals without advanced liver disease have a reduced HRQoL[5]. Important factors reported to influence HRQoL of the general HCV population are stigma, fatigue, and psychological issues such as depression and cognitive impairment[5]. Especially as the majority of HCV-infected persons with hemophilia were infected for at least 30 years, some of these factors may continue to affect their HRQoL.

In line with higher frequency of clotting factor administration and inherent higher risk of HCV infection, severe hemophilia and self-reported joint impairment were more frequent in the HCV-cured group compared with the never chronically infected group. Both factors strongly affect HRQoL of persons with hemophilia[2,3]. Although multivariable analysis was used to adjust for the confounding effect of these variables, residual confounding cannot be excluded. Notably, in the sub-analysis comparing the cured group with the more comparable group of individuals with spontaneous HCV clearance, differences were still seen for all RAND-36 domains except Pain and Emotional well-being.. Therefore, we think that residual confounding alone is insufficient to explain our findings.

To our knowledge, this is the first study on differences in HRQoL between HCV-cured and never chronically HCV-infected persons with hemophilia. In an analysis from the

previous HiN study in 2001, persons with hemophilia with ongoing HCV infection were compared with those never infected with HCV[2]. Statistically significant differences between groups in this HiN-5 study were only reported for the domains General health and Energy/fatigue, while we found differences in seven domains. Several factors may explain this. First, as the previous study was conducted in 2001, infection duration was considerably shorter and advanced fibrosis or cirrhosis was less prevalent than in our study population. Second, unlike in the current analysis, the previous analysis also adjusted for employment status. For the current analysis, we regarded employment as an intermediate effect rather than a confounder and therefore chose not to include it in the multivariable analysis. If adjusted for, the only differences in our analysis would have been the domains General health and Role limitations due to emotional problems (data not shown). Finally, differences in domain scores were interpreted differently between both studies (i.e. based on MID in HiN-6 and based on statistical significance in HiN-5).

Whereas interferon-free DAA treatment in general is well-tolerated, interferon-based therapy was notorious for its severe side-effects, such as fatigue, headache, hair loss and depression[6]. Four weeks after cessation of interferon treatment, fatigue, concentration problems and sleeping problems were still present in over 30% of interferon-treated persons with hemophilia. Even suicidal thoughts were not uncommon (reported to be 4-7% in the general HCV-infected population), although fortunately suicide attempts were rare (0.02%)[20]. Nevertheless, although RAND-36 domain scores significantly decreased during interferon treatment in persons with hemophilia, it was reported that scores approached baseline level within four weeks after treatment cessation[6]. Furthermore, in a study of HCV patients without hemophilia, RAND-36 scores were similar between patients treated with DAA either with or without interferon at 24 weeks post-treatment[21].

This is in line with the findings from our study, with similar RAND-36 domain scores for those ever receiving interferon and those only receiving DAA. In fact, the only difference was in favor of the interferon group, and was found on the Energy/fatigue domain. This difference could have been caused by the selection of patients for interferon therapy, as mental and social stability were prerequisites for interferon therapy, by random variation because of the relatively small numbers in this sub-analysis, or because of a lower prevalence of liver fibrosis in the interferon group (although adjusting for this presence in a sensitivity analysis did not impact results). We did not find evidence for an effect of time since successful treatment on any of the RAND-36 domains within the HCV-cured group. Yet, as residual side-effects of previous interferon treatment were reported in our study by 6% of HCV-cured individuals ever receiving interferon, negative impact of previous interferon treatment on the individual level should not be disregarded.

Therefore, negative side effects of interferon treatment on an individual patient level should be monitored by treating physicians.

Strengths and limitations

To our knowledge, our study is the largest study reporting HRQoL of persons with hemophilia successfully treated for chronic HCV infection, with our sample representing a large part of persons with hemophilia in the Netherlands. Data on severity of hemophilia and HCV status was extracted from medical records, reducing the risk of misclassification as compared with self-reported data. Nevertheless, our study has several limitations. As previously discussed, patient characteristics such as hemophilia severity and joint impairment differed considerably between both groups, and despite multivariable analysis residual confounding cannot be excluded. Furthermore, although all persons with hemophilia known in the Netherlands were invited for the study, only 653 (37%) adults completed the survey and approved data collection from medical records. In the 486 participants included in the current analysis, 99% was aged above 26 years, compared to 67% in the general hemophilia population in the Netherlands[22]. Furthermore, the number of individuals with severe hemophilia in our analysis was slightly lower than in the general Dutch hemophilia population (38% and 54%)[22]. Also, the number of participants with a history of (decompensated) cirrhosis or hepatocellular carcinoma was six (3%), which is smaller than expected based on natural history of HCV[14] and potentially indicates a selection of more healthy subjects in our sample. Furthermore, the interpretation of results depends on the used definition of the MID threshold. The threshold of 4 points was the average of the 3-5 point range that is often used for the MID[18], and comparable to the MID of 4.2 that was set by an expert panel to estimate the MID of the RAND-36 domain Energy/fatigue in HCV[5]. In addition, we were not allowed to collect data on race or ethnicity, which would improve interpretation of our findings relative to other populations. Due to the use of the Dutch version of the SF-36 questionnaire, response rate was likely lower among persons with hemophilia with poor Dutch language skills. We did report other social determinants of HRQoL, i.e. employment and educational status. Finally, the number of included participants with HIV/HCV co-infection or HIV mono-infection was small. Therefore, it is uncertain to what extent our results apply to HIV-infected individuals.

Clinical implications and further research

Our study results emphasize that persons with hemophilia with a history of chronic HCV infection may have limitations on several domains of the RAND-36. We suggest that all HCV-cured persons with hemophilia are screened for the need of extra medical and psychosocial support, with special focus on individuals with HCV infection sequelae, such as advanced fibrosis or cirrhosis. Among patients with liver cirrhosis in

the general population, poor social support is associated with decreased HRQoL[23]. To more specifically assess the needs of persons with hemophilia with an impacted HRQoL following their cured HCV infection, future research that could be of value would be an in-depth qualitative analysis of HRQoL limitations in these persons.

CONCLUSION

Complete HCV elimination among persons with hemophilia in the Netherlands is within reach. However, even after successful HCV treatment, RAND-36 domain scores of HCV cured persons with hemophilia remain lower than scores of those never chronically HCV-infected. Compared with never HCV-infected individuals, the largest differences in domain scores were seen in HCV-cured individuals with cirrhosis or self-reported residual symptoms and on the domains General health, Role limitations due to physical and Role limitations due to emotional problems. Although the differences in characteristics between HCV-cured and never chronically HCV-infected participants preclude any definitive conclusions, our results could imply that residual effects of a cured HCV infection still impact physical, mental or social quality of life domains in some persons with hemophilia and careful medical and psycho-social follow-up and support for these individuals is indicated.

Declaration of interest

C.J. Isfordink has received research funding from Gilead, not related to this study. S.C. Gouw has received unrestricted financial support from Sobi. J.G. van der Bom has been a teacher on the educational activities of Bayer. M. Coppens has received financial support for research from Bayer, CSL Behring, Daiichi Sankyo, Portola/Alexion, Roche, Sanquin Blood Supply and UniQure and consultancy or lecturing fees from Bayer, CSL Behring, Medcon International, MEDtalks, NovoNordisk, Pfizer and Sobi. J. Eikenboom has received research support from CSL Behring (funds to the institute) and an honorarium for educational activity from Roche (funds to the institute). F.W.G. Leebeek received unrestricted research grants from CSL Behring, Shire/Takeda, Sobi and uniQure. He is a consultant for CSL Behring, Shire/Takeda, Biomarin and uniQure, of which the fees go to the University. He received travel support from Sobi. He is DSMB member of a study sponsored by Roche. S.E.M. Schols has received a travel grant from Takeda and an honorarium for educational activity from Takeda and Novo Nordisk. L. van Vulpen has received a grant from CSL Behring and is consultant for Sobi and Tremeau (funds to the institute). All other authors report no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Characteristics of HCV-cured persons with hemophilia and those with spontaneous HCV clearance

	Spontaneous clearance (n=43)	HCV-cured (n=180)
Age (median, IQR)	56 (42 - 67)	57 (47 - 63)
Severity of hemophilia		
Mild	10 (23%)	35 (19%)
Moderate	11 (26%)	25 (14%)
Severe	22 (51%)	120 (67%)
Current use of prophylaxis	18 (42%)	107 (59%)
Joint bleeding in the past 12 months	20 (47%)	91 (51%)
Self-reported joint impairment score (median, IQR)	5 (0 - 10)	2 (7 – 13)
HIV infection	3 (7%)	15 (8%)
Advanced liver fibrosis or cirrhosis*	0	25 (14%)
Employement		
Currently employed / Studying	29 (67%)	94 (52%)
Unemployed	1 (2%)	6 (3%)
Retired	9 (21%)	37 (21%)
Occupational disability	2 (5%)	28 (16%)
Missing/prefer not to say	2 (5%)	15 (8%)

*Fibroscan® value of ≥9.5 kPa or history of liver transplantation, hepatocellular carcinoma or decompensated cirrhosis.
Abbreviations: HCV: hepatitis C virus. IQR: interquartile range.

Supplementary Table 2. Characteristics of HCV-cured and HCV antibody-negative persons with hemophilia

	Never HCV-infected (n=263)	HCV-cured (n=180)
Age (median, IQR)	52 (36 - 63)	57 (47 - 63)
Severity of hemophilia		
Mild	175 (67%)	35 (19%)
Moderate	46 (17%)	25 (14%)
Severe	42 (16%)	120 (67%)
Current use of prophylaxis	47 (18%)	107 (59%)
Joint bleeding in the past 12 months	39 (15%)	91 (51%)
Self-reported joint impairment score (median, IQR)	0 (0 - 1)	2 (7 – 13)
HIV infection	0	15 (8%)
Advanced liver fibrosis or cirrhosis*	0	25 (14%)
Employement		
Currently employed / Studying	181 (69%)	94 (52%)
Unemployed	4 (2%)	6 (3%)
Retired	48 (18%)	37 (21%)
Occupational disability	10 (4%)	28 (16%)
Missing/prefer not to say	20 (8%)	15 (8%)

*Fibroscan® value of ≥9.5 kPa or history of liver transplantation, hepatocellular carcinoma or decompensated cirrhosis.
Abbreviations: HCV: hepatitis C virus. IQR: interquartile range.

Supplementary Table 3. RAND-36 domains scores of HCV-cured and HCV antibody-negative persons with hemophilia

	Never HCV-infected (n=263)	HCV-cured (n=180)	Difference HCV-cured adjusted*	
RAND-36	**mean ±SD**	**mean ±SD**	**Δ**	**95% CI**
General health	67.9 ±20.3	54.1 ±21.8	-9.3	-14.6 - -4.0
Physical functioning	85.1 ±21.2	59.5 ±29.4	-5.5	-10.4 - -0.7
Role physical	83.2 ±32.3	59.1 ±43.1	-14.1	-23.2 - -5.0
Energy/fatigue	67.2 ±16.3	59.8 ±19.2	-7.1	-11.7 - -2.5
Pain	80.9 ±21.0	66.9 ±22.4	-4.4	-9.6 - 0.8
Emotional well-being	80.1 ±13.9	73.8 ±17.8	-8.2	-12.2 - -4.2
Role emotional	89.2 ±26.7	76.6 ±38.0	-11.5	-19.7 - -3.4
Social functioning	86.9 ±18.4	75.9 ±23.1	-7.1	-12.3 - -1.9

HCV: hepatitis C virus. *Adjusted for age, HIV status, self-reported joint impairment and severity of hemophilia. Minimally important difference was established at a difference of 4 points.

PART II

CHALLENGES FOR HEPATITIS C VIRUS ELIMINATION IN PEOPLE LIVING WITH HIV

CHAPTER 5

LOW HEPATITIS C VIRUS-VIREMIA PREVALENCE YET CONTINUED BARRIERS TO DIRECT-ACTING ANTIVIRAL TREATMENT IN PEOPLE LIVING WITH HIV IN THE NETHERLANDS

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On behalf of the ATHENA observational cohort

AIDS, 2022

ABSTRACT

Objective

To describe hepatitis C virus (HCV)-viremia prevalence and barriers to direct-acting antiviral (DAA) treatment during unrestricted access to DAA in a nationwide cohort of people living with HIV (PLWH).

Design

Retrospective analysis of prospectively-collected data.

Methods

We calculated yearly HCV-viremia prevalence as proportion of HCV RNA-positive individuals ever HCV-tested. We then included HCV-viremic individuals with ≥1 visit during the era of universal DAA-access (database lock=31 December 2018). Based on their last visit, individuals were grouped as DAA-treated or -untreated. Variables associated with lack of DAA-treatment were assessed using targeted maximum likelihood estimation. In November 2020, physicians of DAA-untreated individuals completed a questionnaire on barriers to DAA-uptake and onward HCV-transmission risk.

Results

Among 25,196 PLWH, HCV-viremia decreased from 4-5% between 2000-2014 to 0.6% in 2019. Being DAA-untreated was associated with HIV-transmission route other than men who have sex with men, older age, infrequent follow-up, severe alcohol use, detectable HIV-RNA, HCV-genotype 3, and larger hospital size. With universal DAA-access, 72/979 HCV-viremic individuals remained DAA-untreated at their last visit. Of these, 39 were no longer in care, 27 remained DAA-untreated in care, and six initiated DAA since database lock. Most common physician-reported barriers to DAA-uptake were patient refusal (20/72, 28%) and infrequent visit attendance (19/72, 26%). Only one DAA-untreated individual in care was engaging in activities associated with onward HCV-transmission.

Conclusions

Prevalence of HCV-viremic PLWH is low in the Netherlands, coinciding with widespread DAA-uptake. Barriers to DAA-uptake appear mostly patient-related, while HCV-transmission seems unlikely from the few DAA-untreated in care.

INTRODUCTION

Of the recently estimated 38 million people living with HIV (PLWH),[1] approximately 2.3 million are also chronically infected with hepatitis C virus (HCV).[2] After highly effective direct-acting antivirals (DAA) became available,[3] the World Health Organization announced global targets to eliminate HCV, which included attaining treatment uptake in 80% of HCV-infected patients by 2030.[4] Through widespread treatment, HCV can be eliminated by reducing the pool of HCV-infected individuals and consequently preventing ongoing transmission (i.e. treatment as prevention).[5]

The Netherlands began providing universal access to DAA for chronic HCV infection in 2015, after which HCV incidence of PLWH has sharply declined.[6] Nevertheless, according to 2019 estimates, 9% of ever HCV-infected PLWH linked to care in the Netherlands were still HCV-viremic.[7] Coupled with newly occurring acute HCV infections and re-infections, [6] treatment of these remaining HCV-viremic individuals is essential to reduce ongoing HCV transmission and thus achieve micro-elimination. Several studies have examined the reasons why HCV-infected individuals remain untreated.[8–11] However, in those studies DAA treatment was partly restricted or recently unrestricted, making inference to settings with prolonged unrestricted access difficult. Furthermore, the large-scale nature of these cohorts precludes the study of fine-grained reasons surrounding lack of DAA treatment uptake.

The aim of the present study was to describe the prevalence of HCV-viremia in a national cohort of PLWH from 2000-onwards. We examined clinical determinants associated with lack of DAA-uptake in the era of unrestricted access, and, at the individual level, reported main barriers to DAA-uptake and potential risk of ongoing HCV transmission in DAA-untreated PLWH.

METHODS

Study design and setting

This study used data collected in the AIDS Therapy Evaluation in the Netherlands (ATHENA) observational cohort.[12] The ATHENA cohort was initiated in 1998 and has been prospectively collecting data on PLWH in the Netherlands, capturing 98% of all individuals in HIV care from the 24 HIV treatment centers in the Netherlands.[12] Enrolment in the ATHENA cohort is based on an opt-out principle. The institutional review boards of all participating centers approved the cohort. For this study, we included individuals aged 18 years or older at time of enrollment in the ATHENA cohort.

Analyzed study populations

HCV RNA-positive prevalence over time

The yearly prevalence of HCV RNA-positive PLWH in the Netherlands was assessed by including individuals who ever had an HCV RNA or antibody test and had at least one outpatient clinic visit between 2000-2019 (database lock for this analysis was December 31, 2019).

DAA treatment uptake

DAA treatment uptake was assessed by including individuals who had an outpatient clinic visit and were known to be HCV RNA-positive during the era of universal DAA access (defined as the period without any restrictions to DAA access for the treatment of chronic HCV infection, i.e. from October 1, 2015 onwards). Individuals who spontaneously cleared HCV were excluded. Since HCV treatment data are manually collected and verified, resulting in delays, we chose not to use the most recent database lock to select for eligible individuals in this analysis as this might have overestimated the number of DAA-untreated individuals. Thus, we used the database lock of December 31, 2018. Subsequently, HCV treatment data for the individuals selected were updated based on data from the December 31, 2019 database lock (Supplementary Figure 1). Based on data from their last available visit, we then grouped individuals as either DAA-treated (i.e. initiated DAA treatment after October 1, 2015) or DAA-untreated (i.e. never received DAA treatment). These data were used to examine determinants of treatment uptake in the DAA-era.

In-depth questionnaire

More specific reasons for not initiating DAAs at the individual patient level were assessed by sending in-depth questionnaires in November 2020 to the treating physicians or nurses of all those identified as DAA-untreated (Supplementary materials). Data collection also

included information at the last available visit for DAA-untreated individuals who were registered as deceased, moved abroad, or lost to follow-up at database lock.

Covariables

Variables collected from the database were demographic characteristics (age, gender, country/region of origin), alcohol use, body mass index, co-medication use, and hepatitis B virus serology. HIV-related variables included mode of HIV transmission, HIV-1 RNA viral load, CD4 cell count, combination antiretroviral therapy (cART) use, and number of visits. Individuals were assigned to an HCV key population based on their mode of HIV transmission. We considered any MSM who ever injected drugs as part of the MSM key population. HCV-related variables included date of HCV diagnosis, most recent HCV antibody and HCV RNA test results, HCV genotype, and HCV treatment history. Recently acquired HCV infection was defined as a positive HCV RNA or HCV antibody test within one year following a negative RNA or antibody result. Spontaneous clearance was defined as a positive HCV antibody or HCV RNA result, followed by a negative HCV RNA result in the absence of HCV treatment. HCV re-infection was defined as a detectable HCV RNA viral load after previous spontaneous HCV clearance or treatment-induced sustained virological response.

Comorbidities included diabetes, cancer, liver-related morbidity, and cardiovascular disease (i.e. cerebrovascular accident, myocardial infarction, coronary bypass surgery, or a percutaneous coronary stent or dotter procedure). HIV treatment centers were categorized as academic, large non-academic (≥700 PLWH in care), and small non-academic (<700 PLWH in care). Advanced liver fibrosis or cirrhosis was considered to be present if liver stiffness was ≥9.5 kPa or if diagnosed from liver biopsy or radiologic imaging.

Variables collected from the questionnaire included barriers to DAA-uptake, specific socio-economic characteristics, and current risk of onward HCV transmission through sexual risk activities and/or substance use.

Statistical analysis

For the analysis of yearly HCV RNA prevalence, observation time started in 2000 or on the calendar year of the first HIV-related outpatient clinic visit and continued until the calendar year of the last outpatient clinic visit. Prevalence of HCV RNA-positive PLWH in the Netherlands was calculated in calendar year intervals and defined as the proportion of HCV RNA-positive individuals to ever HCV-tested individuals. If an individual had multiple HCV RNA test results within a year, we used the last HCV RNA result from that year. Missing HCV RNA and HCV antibody values were imputed with the most recent

value (i.e. last observation carried forward). If an individual had a negative HCV antibody result with unknown HCV RNA status, we assumed HCV RNA to be negative. If HCV RNA results were missing prior to this negative HCV antibody test, we assumed all HCV RNA tests in preceding years from last HCV RNA test to be negative (i.e. latest observation carried backward). If an individual had a positive HCV antibody result with unknown HCV RNA status, HCV RNA status was analyzed as missing. HCV RNA prevalence per year was then graphed as a smoothed function fit with a locally-weighted regression. These analyses were conducted overall and stratified by MSM and people who inject(ed) drugs (PWID) populations.

For the analysis of determinants of DAA-uptake, characteristics were summarized at the start of DAA therapy for DAA-treated individuals and at the most recent outpatient clinic visit for DAA-untreated individuals. For individuals with re-infection, we only considered data from the most recent re-infection. To measure the association between clinical variables and lack of DAA-uptake, we used targeted maximum likelihood estimation (TMLE)[13,14] to estimate the target parameter of an odds ratio (OR) along with its 95% confidence intervals (CI) from binary exposure and binary outcome variables. The method is robust against misspecification of the exposure and outcome mechanisms and includes a step in which the bias-variance tradeoff is optimized for the parameter of interest using an ensemble of machine learning techniques, referred to as a "super learner.[15] Estimates were constructed using the "tmle" and "SuperLearner" packages in R. We used a collection of machine learning algorithms, defined as ensembles, to estimate the outcome regression and propensity score regression components of the TMLE procedure. The ensembles included the following methods: generalized linear models (with and without interactions), generalized additive models, regression trees, random forests (minimum node sizes of 50, 100, 150 and 200 individuals), extreme gradient boosting (with the same node specifications as in the random forests with combinations of shrinkage parameters at 0.001, 0.01 and 0.1), and elastic net regression (alpha at 0, 0.2, 0.4, 0.6, 0.8 and 1). Data were analyzed using R (version 3.6.1, Vienna, Austria).

RESULTS

Prevalence of HCV RNA-positive individuals

In total 25,059 individuals in the ATHENA cohort linked to care for at least one year since 2000 were ever tested for HCV and if HCV antibody positive, had a known HCV RNA test result (Supplementary Figure 2). Participant characteristics stratified by lost to follow-up status are given in Supplementary table 1. Individuals who were lost to follow-up less often belonged to the MSM key population, were more often of non-Dutch origin and were more frequently HCV RNA-positive at the end of follow-up. The end of follow-up was before unrestricted DAA access for 70% and 13% of individuals who were lost to follow-up and not lost to follow-up, respectively. The proportion of HCV RNA-positive individuals among the PLWH ever tested for HCV remained stable between 4.0% and 5.0% from 2000 to 2014 (Figure 1a). In 2015, the overall prevalence was 4.2% and steeply decreased to 1.6% in 2016, reaching 0.6% in 2019. Decreases were also observed in MSM, with a decline from 3.9% in 2015 to 0.5% in 2019 (Figure 1b), and in PWID, with a decline from 52% in 2015 to 12% in 2019 (Figure 1c).

DAA treatment uptake in the era of universal access

During the era of universal DAA-access, 1031 individuals had ≥1 outpatient clinic visit with a positive HCV RNA result (Supplementary Figure 3). After excluding individuals with spontaneous HCV clearance, 1002 remained, of whom 911 were DAA-treated and 91 were DAA-untreated at their last visit. Nineteen untreated individuals were excluded from further analysis as they were deceased (*n*=11), had moved abroad (*n*=7), or were lost to follow-up (*n*=1) within six months after start of the DAA era or after their HCV diagnosis in the DAA era (i.e. insufficient time to initiate DAA treatment). Four DAA-treated individuals who were not re-treated after prior unsuccessful DAA treatment despite more than one year follow-up after end of treatment (i.e. inconsistent reasons for DAA uptake) were also excluded from this analysis. In total, 72 untreated and 907 treated individuals were included in the analysis of DAA-uptake.

The characteristics of DAA-treated and DAA-untreated individuals are summarized in Table 1. Using targeted maximum likelihood estimation, factors that were associated with lack of DAA treatment were belonging to a key population other than MSM, older age, on average less than one outpatient clinic visit per seven months), alcohol use>20 units per week, having a detectable HIV RNA, HCV genotype 3, using anticonvulsants or proton pump inhibitors, and hospital size (Table 2).

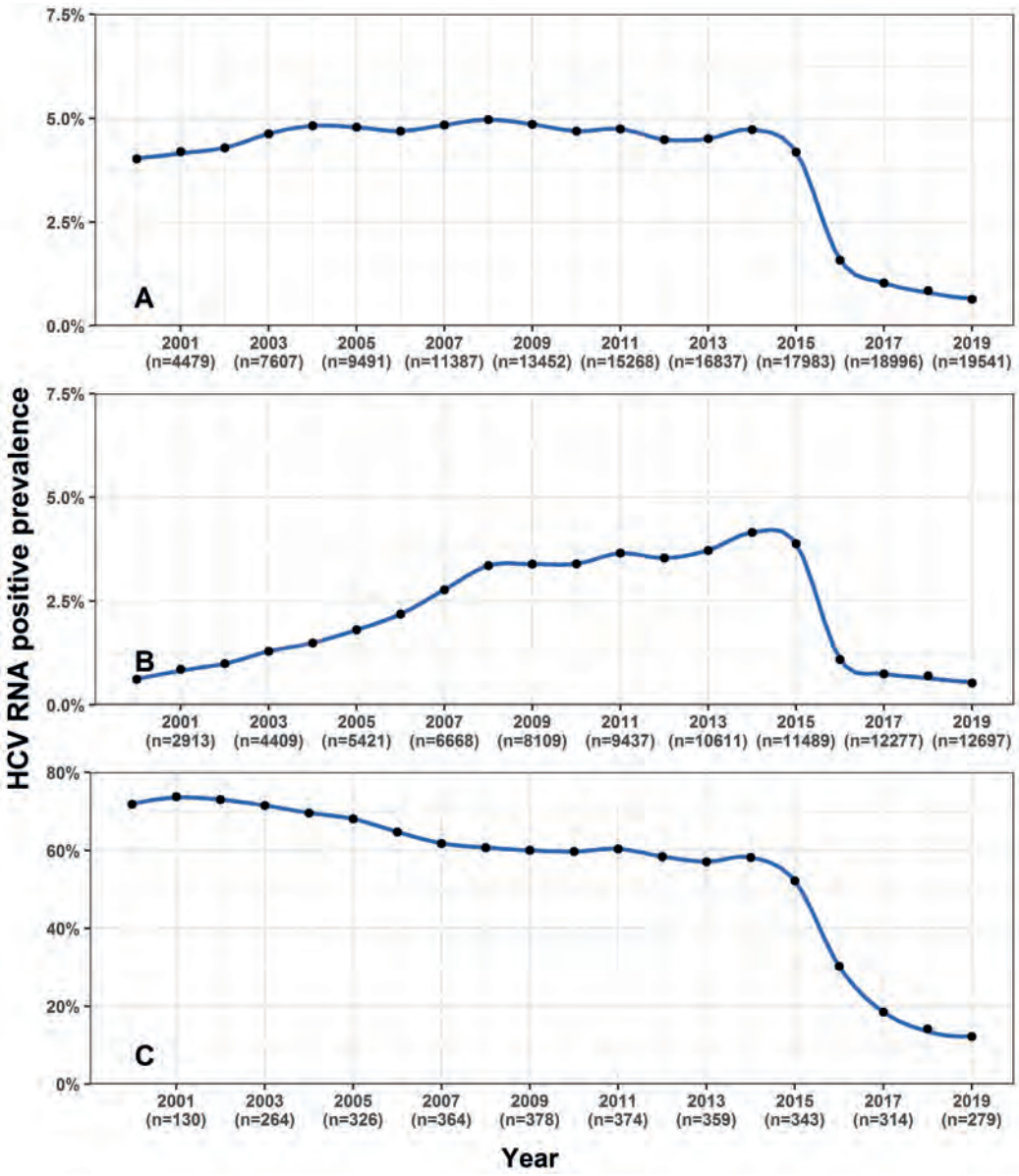

Figure 1. HCV RNA-positive prevalence among HIV-positive individuals tested for HCV in in the Netherlands from 2000 to 2019

Prevalence of HCV RNA-positive persons with HIV included in the ATHENA cohort overall (A), and stratified by men who have sex with men (B) and people who inject drugs (C). Numbers in parenthesis represent the number of individuals with a known HCV RNA status linked to care during that year. Abbreviations: HCV: hepatitis C virus. PLWH: people living with HIV.

Table 1. Baseline characteristics of included participants, according to DAA treatment uptake

	DAA-untreated (*n*=72)	DAA-treated (*n*=907)
Male sex	56 (78%)	820 (90%)
Age (median, IQR)	54 (47 – 61)	48 (42 – 55)
HIV transmission route		
MSM	13 (18%)	657 (72%)
IDU	41 (57%)	125 (14%)
Heterosexual	8 (11%)	68 (8%)
Blood	0	8 (1%)
Other	10 (14%)	49 (5%)
Non-Dutch origin	32 (44%)	332 (37%)
HIV RNA undetectable (<50 copies/ml)	54 (75%)	835 (92%)
CD4 count (median, IQR)	450 (255 – 715)	643 (478 – 840)
Average <1 visit per 7 months follow-up in DAA era	27 (38%)	40 (4%)
Weekly alcohol use		
None	19 (26%)	229 (25%)
1-20 units	25 (35%)	466 (51%)
>20 units	13 (18%)	74 (8%)
Unknown	15 (21%)	138 (15%)
Center		
Small non-academic	8 (11%)	110 (12%)
Large non-academic	23 (32%)	477 (53%)
Academic	41 (57%)	320 (35%)
HCV genotype		
1	32 (44%)	575 (63%)
3	22 (31%)	61 (7%)
4	9 (13%)	179 (20%)
Other	3 (4%)	33 (4%)
Missing	6 (8%)	59 (7%)
Type of HCV infection		
1st infection, chronic at diagnosis	65 (90%)	461 (51%)
1st infection, acute at diagnosis	6 (8%)	305 (34%)
Re-infection	1 (1%)	139 (15%)
Years since HCV diagnosis (median, IQR)	14 (7 – 19)	3 (1 – 9)
(PEG-)IFN treatment experience	12 (17%)	259 (29%)
Advanced fibrosis or cirrhosis	7 (10%)	72 (8%)
Anticonvulsant use	10 (14%)	31 (3%)
Proton pump inhibitor use	24 (33%)	91 (10%)

Data are reported as number (percentage) unless otherwise noted. Characteristics were summarized at the start of DAA therapy for DAA-treated individuals and at the most recent outpatient clinic visit for DAA-untreated individuals.

Abbreviations: DAA: direct-acting antivirals. MSM: men who have sex with men. IDU: injecting drug use. HCV: hepatitis C virus. (PEG-)IFN: (Pegylated-)Interferon.

Table 2. Targeted maximum likelihood estimation analysis of lack of DAA treatment uptake and clinical covariates

	Association with remaining DAA-untreated*	
	Odds ratio	**95% CI**
Transmission route / gender		
MSM	Ref	
IDU, female	5.2	2.6 – 10.2
IDU, male	9.6	5.1 – 18.1
Other, female	2.9	1.2 – 7.0
Other, male	4.8	1.5 – 15.0
Age, tertiles		
Low (<=44.7 years)	Ref	
Middle	1.2	0.6 – 2.2
High (>=53.0 years)	1.9	1.2 – 3.2
Non-Dutch versus Dutch origin	0.9	0.6 – 1.3
HIV RNA undetectable versus detectable	0.4	0.3 – 0.6
Average <1 versus ≥1 visit per 7 months follow-up in DAA era	9.7	5.5 – 17.1
Alcohol use		
≤20 units per week	Ref	
>20 units per week	1.9	1.2 – 3.0
Missing	0.8	0.6 – 1.2
HCV genotype 3 versus other	1.7	1.2 – 2.5
Acute infection or re-infection at diagnosis, versus chronic infection at diagnosis	0.4	0.1 – 1.3
Advanced fibrosis or cirrhosis		
No	Ref	
Yes	0.9	0.6 – 1.4
Missing	1.7	1.1 – 2.5
Anticonvulsant / Proton Pump Inhibitor use	1.5	1.1 – 2.1
Center		
Academic	Ref	
Large non-academic	0.5	0.4 – 0.8
Small non-academic	0.6	0.3 – 0.9

*Analyzed using targeted maximum likelihood estimation.
Abbreviations: OR: odds ratio. MSM: men who have sex with men. IDU: injecting drug use. DAA: direct-acting antivirals. HCV: hepatitis C virus.

Barriers to DAA treatment uptake

Of the 72 DAA-untreated individuals, 63 in-depth questionnaires (88%) were returned between November 2020 and March 2021 (2 forms not returned, 7 individuals had been in care in two hospitals that closed at the end of 2018 and hence their physician could not be approached with the additional in-depth questionnaire). Of the 72 DAA-untreated individuals, 39 were no longer in care (Supplementary table 2; deceased, *n*=22; lost to follow-up, *n*=11; moved abroad, *n*=6), while six initiated DAA after the last database update. The remaining 27 were still DAA-untreated (52% injecting drug use (IDU); 26% MSM, 22% other) and in care in November 2020. Of those who died, the most frequent causes of death were pulmonary disease (n=6, 27%), non-AIDS/non-hepatic-related malignancies(n=4, 18%), and liver-related death (n=2, 9%).

When analyzing the complete group of 72 DAA-untreated individuals, the most common barriers to DAA-uptake reported by physicians were patient refusal (*n*=20, 28%), infrequent visit attendance (*n*=19, 26%), and the absence of liver fibrosis (*n*=18, 25%) (Table 3). Only two individuals were reported to be at risk of transmitting HCV through substance use, and no DAA-untreated individual was reported to engage in sexual activities associated with onward HCV transmission. In-depth questionnaires were also sent to treating physicians of the four individuals who did not receive retreatment after DAA failure, of whom three forms were returned. Of these four individuals two were still in care, one was lost to follow-up and one was deceased. The reasons for lack of retreatment were patient refusal (n=1), patient-experienced DAA intolerance (n=1), and retreatment not possible due to resistance associated substitutions (n=1). The currently lost to follow-up individual that refused retreatment was assessed to be at risk of onward HCV transmission through both substance use and sexual activities.

When focusing on the group of 27 DAA-untreated individuals still in care in the Netherlands (Table 3; 1 form not returned, 4 individuals were in care at one of the closed hospitals), the most commonly reported barriers to lack of DAA treatment uptake remained patient refusal (*n*=11, 41%), no liver fibrosis and infrequent visit attendance (both *n*=7, 26%), and severe comorbidity (*n*=6, 22%). Multiple barriers were reported in 13 individuals (Table 4). As assessed by physicians, one remaining DAA-untreated individual in care was reported to engage in activities potentially associated with risk of onward HCV transmission through substance use.

Table 3. Physician-reported barriers to DAA treatment and risk of onward transmission in HIV-positive individuals known as DAA-untreated in the era of universal access to DAA

	Still in care			
	DAA-untreated (n=27)	**Successfully treated after dataset update (n=6)**	**No longer in care* (n=39)**	**Total (n=72)**
Barrier to treatment uptake[$]				
Patient refusal	11 (41%)	2 (33%)	7 (18%)	**20 (28%)**
Infrequent visit attendance	7 (26%)	1 (17%)	11 (28%)	**19 (26%)**
No liver fibrosis	7 (26%)	1 (17%)	10 (26%)	**18 (25%)**
Insufficient adherence expected	4 (15%)	1 (17%)	11 (28%)	**16 (22%)**
Severe comorbidity	6 (22%)	1 (17%)	6 (15%)	**13 (18%)**
No permanent residence	0	1 (17%)	4 (10%)	**5 (7%)**
Instable psychosocial situation	1 (4%)	2 (33%)	2 (5%)	**5 (7%)**
Reason unknown	0	0	5 (13%)	**5 (7%)**
Other reason	6 (22%)	1 (17%)	2 (5%)	**17 (24%)[^]**
Advanced liver fibrosis or cirrhosis	5 (19%)	0	6 (15%)	**11 (15%)**
Socioeconomic characteristics[#]				
Permanent residence	19 / 20 (95%)	not asked	19 / 25 (76%)	**38 / 45 (84%)**
Health insurance	21 / 21 (100%)	not asked	19 / 25 (76%)	**40 / 46 (87%)**
Employed / retired	5 / 19 (26%)	not asked	7 / 26 (27%)	**12 / 45 (27%)**
Regular income	8 / 13 (62%)	not asked	6 / 19 (32%)	**14 / 32 (44%)**
Regular partner	4 / 14 (29%)	not asked	7 / 16 (44%)	**11 / 37 (37%)**
Physician-reported risk of onward sexual HCV transmission[#]	0 / 16 (0%)	0	0 / 35 (0%)	**0 / 51 (0%)**
Physician-reported risk of onward HCV transmission through substance use[#]	1 / 18 (6%)	0	1 / 35 (3%)	**2 / 53 (4%)**
In-depth questionnaire missing	5 (19%)	0	4 (10%)	**9 (13%)[+]**

Data obtained via questionnaire by the treating physician (December 2020 - March 2021). *Either deceased (n=22), moved abroad (n=6) or lost to follow-up (n=11). [$]Multiple barriers per individual are possible. [^]Other reasons: health insurance issues (*n*=4), alcohol and/or substance abuse (*n*=3), very low HCV viral load (*n*=2), no risk of onward HCV transmission (*n*=2), high age (*n*=1), language barrier (*n*=1), antiretroviral therapy switch required first (*n*=1), lives in multiple countries, not long enough in the Netherlands for HCV treatment (*n*=1), moved abroad (*n*=1), received HIV care through general practitioner for several years (*n*=1). [#]Denominator is the number of individuals with a known status (i.e. yes or no answered). Remaining DAA-untreated individuals have an unknown or missing status. [+]Two forms not returned, 7 individuals were in care in two hospitals that closed at the end of 2018 and hence their data were not available for the additional in-depth questionnaire. Abbreviations: DAA: direct-acting antivirals. HCV: hepatitis C virus. LTFU: Lost to follow-up.

Table 4. Physician-reported barriers to DAA treatment and risk of onward transmission in the remaining DAA-untreated HIV-positive individuals linked to care in the Netherlands

	Advanced fibrosis/ cirrhosis	Years since HCV diagnosis	Reported barriers to DAA treatment uptake	Risk of onward HCV transmission
Key population: men who have sex with men				
1	No	7	Infrequent visit attendance	Unknown
2	Unknown	3	Repeatedly low HCV RNA viral load (<10 to 40 IU/ml)	Substance use no, sexual unknown
3	No	13	Refusal, no fibrosis	Substance use no, sexual unknown
4	No	3	Refusal, infrequent visit attendance, frequent visits to country of origin	Unknown
Key population: people who ever injected drugs				
5	Yes	24	Refusal	Substance use no, sexual unknown
6	No	19	Severe comorbidity, infrequent visit attendance	No
7	No	22	Severe comorbidity, no fibrosis	No
8	Yes	19	Severe comorbidity	No
9	Yes	22	Refusal	No
10	No	17	No fibrosis, no risk of transmission	No
11	Yes, previously decompensated	15	Severe comorbidity, insufficient adherence expected, infrequent visit attendance, risk of decompensation during treatment, limited health gain expected in patient with cirrhosis and ongoing alcohol use	No
12	No	12	Refusal, unstable psychosocial situation, patient not motivated, insufficient adherence expected	No
13	No	11	Infrequent visit attendance	Yes, through substance use
14	No	11	Low HCV RNA viral load (200 IU/ml), no fibrosis, language barrier	No
15	No	26	Severe comorbidity, insufficient adherence expected, infrequent visit attendance	No
16	Unknown	21	Refusal	No

Table 4. Physician-reported barriers to DAA treatment and risk of onward transmission in the remaining DAA-untreated HIV-positive individuals linked to care in the Netherlands (continued)

	Advanced fibrosis/ cirrhosis	Years since HCV diagnosis	Reported barriers to DAA treatment uptake	Risk of onward HCV transmission
Key population: other				
17	No	28	Refusal	Unknown
18	No	14	Refusal, no fibrosis	No
19	No	20	Refusal	No
20	No	19	Insufficient adherence expected, infrequent visit attendance, no fibrosis	Substance use no, sexual unknown
21	No	25	Refusal, no fibrosis	No
22	Yes	19	Refusal, severe comorbidity	No

Results from in-depth data collection of 22/27 remaining DAA-untreated individuals of the study cohort still linked to care. Data obtained via questionnaire by the treating physician (November 2020 - March 2021).
Abbreviations: DAA: direct-acting antivirals. HCV: hepatitis C virus.

DISCUSSION

The introduction of DAA has made HCV micro-elimination in PLWH a feasible goal in the Netherlands. Following universal access to DAA and subsequent widespread DAA-uptake, HCV RNA-positive prevalence in PLWH in the Netherlands decreased sharply from 2016 onwards. As a result, HCV RNA-positive prevalence was 0.6% at the end of 2019 and only 3% (n=27/979) of all individuals with a positive HCV RNA during the DAA-era remained DAA-untreated and were still in care as of November 2020. In-depth questionnaires revealed several physician-reported barriers to DAA-uptake that might be difficult for treating physicians to overcome. Very few DAA-untreated individuals appeared to engage in activities associated with risk of onward HCV transmission.

Importantly, PWIDs more frequently remained DAA-untreated in our study, which is reflected by the 12% prevalence of HCV RNA-positive PWIDs in 2019. To our knowledge, only one prior study regarding DAA-uptake in HIV/HCV co-infected individuals was conducted completely within a time period of universal DAA access.[16] In contrast to our findings, current or former injecting drug use (IDU) was not associated with lack of DAA-uptake in this Australian study.[16] In that study, current injecting (meth)amphetamine use was common among MSM (35%), whereas IDU in MSM in the Netherlands is infrequent and likely ranges from 1% (in sexually active MSM overall)[17] to 8% (in HIV-positive individuals at risk of HCV re-infection).[18] Furthermore, DAA-uptake was not compared between the MSM and PWID key populations in the Australian study, which might be difficult because of the highly overlapping transmission routes in their setting.

Another explanation for this difference could be the Australian system of decentralized DAA prescriptions, which could lower the threshold to HCV treatment for hard-to-reach subgroups and reduce dependency on regular outpatient clinic visits. The proportion of DAA-treated HCV-infected patients achieving SVR in these programs has been shown to be comparable to those when prescribing is done by specialists.[19] Unfortunately, decentralized prescribing of DAA outside of a hospital outpatient clinic is not yet possible in the Netherlands. In our study, infrequent visit attendance was independently associated with lack of DAA-uptake and reported as a barrier to DAA-uptake in 25% of DAA-untreated individuals. Almost half of the DAA-untreated individuals in our study were using methadone, generally provided by methadone outposts or general practitioners, which could be ideal places to provide HCV treatment for these few individuals left behind. A cluster-randomized trial in Scotland reported a significantly higher rate of HCV testing, DAA initiation and SVR-12 for individuals receiving opioid substitution therapy with HCV care led by pharmacists versus conventional care.[20] These programs would appear essential for HCV elimination in the Netherlands.

Among studies conducted in settings without universal DAA-access, individuals with frequently missed visits and PWID were less likely to receive DAA,[8–11] similar to our findings. Additionally, those with advanced fibrosis or cirrhosis more often received DAAs, likely owing to the specific restrictions put in place in these settings.[8–11] Regarding alcohol use, similar to what we observed, severe alcohol use was associated with a lower DAA-uptake in a study in HCV-infected individuals receiving opioid agonist therapy,[21] which was not confirmed in a smaller study among HIV-positive PWID.[22] Of note, both studies analyzed severe alcohol use at a cut-off that was higher than the cut-off of >20 units/week in our cohort. As alcohol abuse is associated with accelerated progression of liver fibrosis in HCV-infected individuals,[23] improving DAA-uptake in this group is important to reduce liver-related morbidity and mortality.

Due to widespread harm reduction services and a low number of active injecting drug users in the Netherlands, incidence rates of new HCV infections in HIV-positive PWID have remained low for many years.[6] Conversely, we recently reported that despite a clear overall decrease in the incidence of primary HCV infection and re-infection in HIV-positive MSM, it remains significant at 4 and 11 per 1000 person-years, respectively.[6] Despite these differences in incidence rates, PWID had a substantially higher prevalence of individuals currently HCV RNA-positive compared to MSM. This seemingly contradictory finding could be explained by the lower risk of onward HCV transmission and lower DAA-uptake in PWID, as observed in our study, and the likely higher proportion of MSM engaging in at risk activities and higher DAA-uptake in MSM.[6,24] Our results highlight incongruity with the goals needed for elimination – as PWID seem to be left behind in treatment scale-up programs. We believe elimination should focus not only on HCV incidence, but also on HCV RNA-positive prevalence and more attention is needed to treat all HCV RNA-positive individuals, including those who were not recently diagnosed with HCV. Enabling decentralized DAA treatment and integration of HCV treatment into addiction care seem key to reach the more difficult to reach in our setting.

Our study included data from a large cohort involving nearly all PLWH in care in the Netherlands. Furthermore, a recent capture-recapture analysis showed that between 2013 and 2016 99% of acute HCV infections of HIV-positive individuals registered in the Dutch National Registry for Notifiable Diseases were captured in the ATHENA cohort.[25] Thus, we believe that the coverage of data offered by the ATHENA cohort is sufficient to understand issues related to DAA treatment access at a wide-reaching level. Additionally, we report in-depth data from questionnaires that are difficult to obtain from large-scale studies. Nevertheless, several limitations apply to our study. First, regarding the prevalence of HCV-viremia, 135 PLWH with positive HCV antibodies were excluded as their HCV RNA status was unknown. Most of these individuals were either linked to care

for a limited number of years before the DAA era (75%) or had tested HCV antibody positive directly prior to the database lock in 2019 (10%), and therefore lacked HCV RNA confirmation due to an awaiting HCV RNA result. In addition, although EACS guidelines recommend regular testing for HCV in those with HCV-related risk behavior,[24] we were unable to evaluate health care provider adherence to these guidelines. In the MSM key population, the proportion that had at least one HCV test during the calendar year was 32-43% between 2008 and 2019[6]; however, data could not be stratified by risk behavior. Therefore, the reported prevalence of HCV RNA-positive individuals could have been underestimated. Gaining insight in the population that does not have annual HCV testing and increasing the HCV testing rate are important considerations for future research. Second, 12 DAA-untreated individuals in our study were lost to follow-up as of November 2020 and despite our efforts, we were unable to obtain further information on these individuals. Importantly, the majority of the DAA-untreated persons in our group did receive adequate medical care for HIV, as 85% were prescribed HIV treatment and 75% had an undetectable HIV RNA. Individuals who are LTFU are likely to be HIV- or HCV-viraemic individuals and could be an important driver for ongoing HIV- and HCV transmission, thereby underlining the necessity of interventions improving engagement in care for these individuals. In the Netherlands, a nationwide project aiming to retrieve individuals who were previously diagnosed with HIV/HCV or HCV mono-infection but no longer engaged in care is currently ongoing.[26]

Third, for practical reasons, our study did not include those diagnosed with HCV after May 2019. Nonetheless, since ongoing HCV transmission in PLWH in the Netherlands is almost exclusively seen in MSM,[6] who have a high DAA-uptake, we expect the risk of remaining DAA-untreated for newly HCV-diagnosed individuals to be low. In fact, almost all DAA-untreated individuals in our cohort were diagnosed with HCV infection prior to universal DAA access. Fourth, individuals who were lost to follow-up were more frequently HCV RNA-positive at the end of follow-up, which could indicate differential lost to follow-up bias. However, this difference was likely also affected by the fact that individuals who were lost to follow-up more often had their end of follow-up before unrestricted DAA access. Fifth, the barriers to DAA uptake obtained from in-depth questionnaires were physician-reported and might not adequately reflect the barriers that patients experience. Some barriers, such as patient refusal, can be ambiguous and have many underlying factors. Moreover, physicians were unable to report whether all untreated individuals were engaging in activities associated with HCV transmission, potentially underestimating the extent of high risk behavior in this group. Sixth, some of the found associations between clinical variables, particularly HCV genotype 3 infection or hospital type, and remaining DAA-untreated could be biased by residual confounding of unmeasured covariates. Based on an E-value analysis,[27] it would require an association

of 2.8 or higher (E-value for lower limit of 95% CI 1.7) of an unmeasured confounder to explain away the association between HCV genotype 3 infection and remaining DAA-untreated conditional on the included co-variates. For hospital size, E-values were 2.8 (upper limit of 95% CI 1.8) and 2.3 (upper limit of 95% CI 1.4) for large and small non-academic centers, respectively. Finally, the factors associated with a lack of DAA-uptake might be different in countries with different healthcare settings or different HIV/HCV epidemiology.

In conclusion, the current prevalence of HCV RNA-positive HIV-positive individuals in care is low in the Netherlands, coinciding with widespread DAA-uptake. This shows that in settings where DAA access is universal, HCV RNA prevalence can be reduced at population level, highlighting the feasibility of HCV elimination in PLWH. Several factors associated with a lower DAA treatment uptake were found, including belonging to the key population of PWID and a low frequency of hospital visits. Physician-reported barriers to DAA-uptake were heterogeneous, with patient refusal being most frequently reported. The low HCV-viremia prevalence alongside the steep decline in incidence of primary HCV infections and HCV re-infections[6] and presumed limited risk of ongoing forward HCV transmission of remaining DAA-untreated individuals demonstrate that the Netherlands is close to HCV micro-elimination in the population of PLWH. Yet, more attention is required to those remaining HCV RNA-positive.

Declaration of interest

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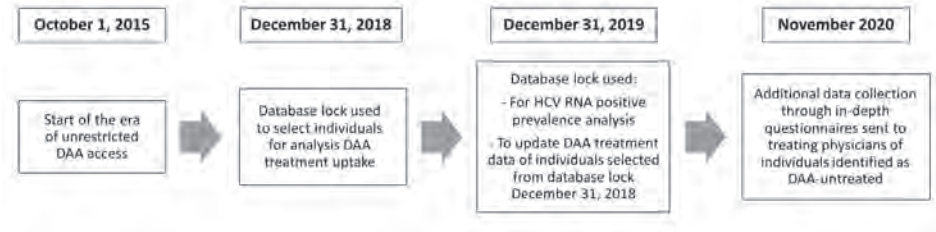
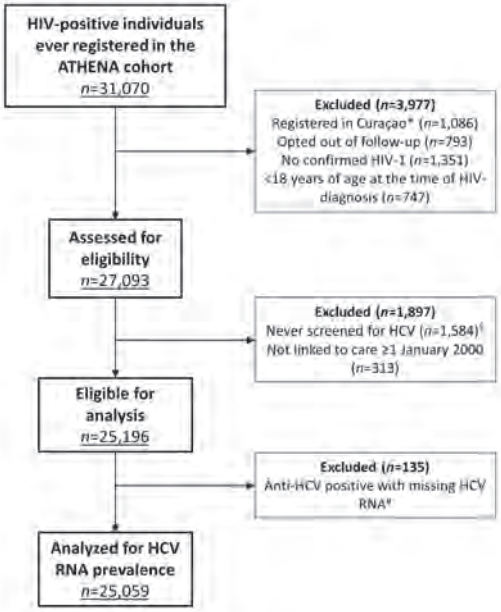
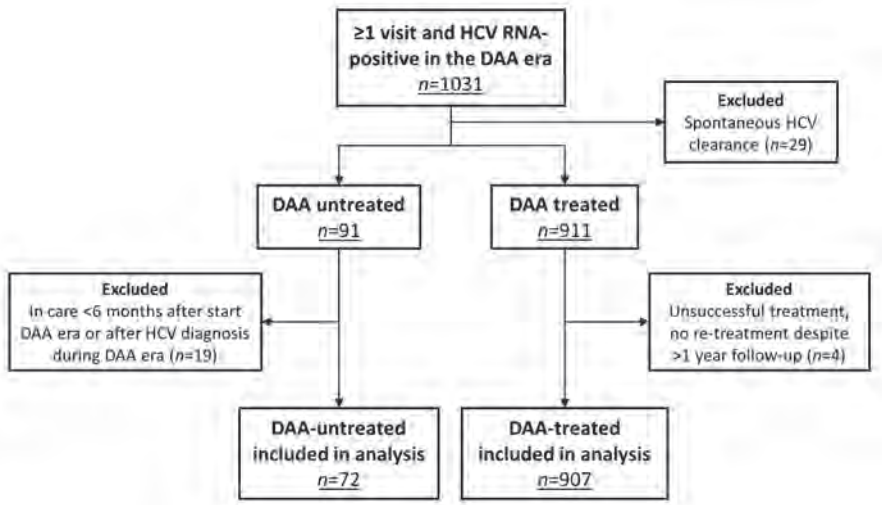
SUPPLEMENTARY MATERIAL



Supplementary figure 1. Analysis timeline
More information on the cohort profile and structure can be found elsewhere[1]. Abbreviations: DAA: direct-acting antivirals. HCV: hepatitis C virus.



Supplementary figure 2. Flowchart for the selection of individuals included in the analysis of HCV RNA-positive prevalence in people living with HIV in the Netherlands
More data on HIV quality of care indicators of individual centers can be found in chapter 7 of the Dutch HIV monitoring report[2]. *Excluded as these individuals are linked to HIV care outside of the country of the Netherlands. §These individuals were more likely to have discontinued care after January 1, 2006 (when HCV screening was infrequent) or have acquired HIV through heterosexual or unknown transmission routes compared to those screened.[2] #69 died, 13 lost to follow-up, 10 moved abroad. These were mainly individuals who were either linked to care for a limited number of years and before the DAA era (75%) or tested HCV antibody positive near the database lock in 2019 (10%). Abbreviations: HCV: hepatitis C virus.



Supplementary Figure 3. Flowchart DAA treatment uptake in HIV-positive individuals in the Netherlands

Abbreviations: HCV: hepatitis C virus. DAA: direct-acting antivirals.

Supplementary table 1. Participant characteristics at the start and end of follow-up, stratified by lost to follow-up status

	Total population (n=25196)	LTFU participants (n=1410)	Non-LTFU participants* (n=23786)
Mode of HIV transmission			
MSM	15425 (61%)	508 (36%)	14917 (63%)
IDU	709 (3%)	63 (4%)	646 (3%)
Heterosexual	7457 (30%)	675 (48%)	6782 (29%)
Blood	299 (1%)	18 (1%)	281 (1%)
Other	1296 (5%)	146 (10%)	1160 (5%)
AIDS at HIV diagnosis	3446 (14%)	165 (12%)	3281 (14%)
Non-Dutch origin	11189 (44%)	1104 (78%)	10085 (42%)
Characteristics at the start of follow-up$			
Age (median, IQR)	39 (32 - 46)	34 (28 - 41)	39 (32 - 47)
Ever AIDS	4074 (16%)	208 (15%)	3866 (16%)
CD4 count (median, IQR)	410 (240 - 610)	384 (234 - 580)	410 (240 - 610)
Ever C-ART prescribed	9284 (37%)	520 (37%)	8764 (37%)
HIV RNA undetectable (<50 copies/ml)	5340 (21%)	299 (21%)	5041 (21%)
HCV infection status			
HCV antibody negative	20118 (80%)	1124 (80%)	18994 (80%)
HCV RNA negative	784 (3%)	43 (3%)	741 (3%)
HCV RNA positive	706 (3%)	85 (6%)	621 (3%)
HCV antibody positive, RNA missing	472 (2%)	31 (2%)	441 (2%)
Not tested	3116 (12%)	127 (9%)	2989 (13%)
Characteristics at the end of follow-up			
Age (median, IQR)	50 (40 - 58)	39 (32 - 47)	50 (41 - 58)
Ever AIDS	6548 (26%)	305 (22%)	6243 (26%)
CD4 count (median, IQR)	640 (442 - 860)	475 (311 - 680)	650 (455 - 870)
Ever C-ART prescribed	24281 (96%)	1103 (78%)	23178 (100%)
HIV RNA undetectable (<50 copies/ml)	21326 (85%)	742 (53%)	20584 (87%)
HCV infection status			
HCV antibody negative	22486 (89%)	1220 (87%)	21266 (89%)
HCV RNA negative	2040 (8%)	75 (5%)	1965 (8%)
HCV RNA positive	535 (2%)	102 (7%)	433 (2%)
HCV antibody positive, RNA missing	135 (1%)	13 (1%)	122 (1%)
Not tested	0	0	0
End of follow-up before unrestricted DAA access	4054 (16%)	983 (70%)	3071 (13%)

*Including participants deceased or moved abroad. $Start of follow-up for the HCV viremia prevalence analysis, i.e. January 1, 2000 or the first visit if on a later date.

Abbreviations: LTFU: Lost to follow-up. MSM: men who have sex with men. IDU: injecting drug use. AIDS: acquired immune deficiency syndrome. C-ART: combined antiretroviral therapy. HCV: hepatitis C virus.

Supplementary table 2. Participant status stratified by DAA treatment uptake

	DAA-untreated (*n*=72)	DAA-treated (*n*=907)
Status*		
In care	33[$] (46%)	838 (92%)
Deceased	22 (31%)	23 (3%)
Lost to follow-up	11 (15%)	11 (1%)
Moved abroad	6 (8%)	28 (3%)

*For DAA-untreated individuals: last known status from the database lock, updated with data from the questionnaires. For DAA-treated individuals: last known status from the database lock. [$]Six individuals started DAA treatment after the last database lock.
Abbreviations: DAA: direct-acting antivirals

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CHAPTER 6

REASONS FOR NOT RECEIVING DIRECT-ACTING ANTIVIRALS DESPITE UNIVERSAL ACCESS FOR INDIVIDUALS WITH HIV/HCV: A MULTINATIONAL COHORT STUDY

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on behalf of the InCHEHC study group

Submitted

ABSTRACT

Introduction

Individuals with HIV/hepatitis C virus (HCV) who remain untreated with direct-acting antivirals (DAA) can still contribute to HCV transmission and HCV-related mortality. We aimed to compare rates of DAA-uptake following universal DAA-access in various countries and to examine factors associated with remaining DAA-untreated.

Methods

We analyzed data from nine observational cohorts participating in the International Collaboration on Hepatitis C Elimination in HIV Cohorts (InCHEHC), including data from six countries. We included individuals with HIV and HCV (i.e., positive HCV RNA without evidence of spontaneous clearance) during unrestricted access to interferon-free DAA-treatment. We calculated the cumulative proportion remaining DAA-untreated after the date of unrestricted access or cohort inclusion, whichever occurred most recently. Determinants associated with DAA initiation rate were assessed using competing-risks regression.

Results

We included 4,552 individuals with HIV/HCV, mainly men who have sex with men (MSM, *n*=2,156;47%) and people who inject(ed) drugs (*n*=1,453;32%). During a median follow-up of 7.3 months (IQR=2.3-19.5), 3,187/4,552 (70%) initiated DAA-treatment. Being linked to care in Australia, France or the Netherlands, on antiretroviral therapy, having undetectable HIV RNA and longer duration since first positive HCV test were independently associated with higher DAA initiation rate. Compared to MSM, male heterosexuals or females with HIV transmission route other than injecting drug use or heterosexual transmission were associated with lower DAA initiation rate.

Conclusion

Despite universal access, 30% of individuals with HIV/HCV remained DAA-untreated during follow-up, with inconsistency in DAA initiation rate between countries and key populations. Increased efforts are required to reach the remaining HCV-viremic individuals with HIV and achieve HCV micro-elimination.

INTRODUCTION

According to the most recent global estimates, 38 million persons are living with HIV and approximately 2.3 million are living with HIV/hepatitis C virus (HCV).[1,2] Since access to highly effective[3] direct-acting antiviral (DAA) therapy for the treatment of HCV has become unrestricted in many high-income settings, there have been rapid increases in HCV treatment coverage[4,5] and subsequently sharp decreases in HCV incidence[6–8] and proportion of HCV-viremic individuals[4,9,10] among people living with HIV.

Nevertheless, treatment uptake has attenuated after the initially rapid uptake reached a large part of the population in need of treatment.[4,5] The fact that some individuals remain untreated even in the context of universal access suggests certain barriers to DAA treatment and could imply harder-to-treat populations exist. As these individuals might still contribute to ongoing HCV transmission and are still at risk of HCV-related mortality, their treatment uptake is critical to achieving HCV micro-elimination in people living with HIV.

In several national and regional cohort studies, investigators have examined factors associated with lack of DAA treatment uptake in individuals with HIV/HCV.[4,9,11,12] Among these factors were belonging to key populations other than men who have sex with men (MSM), having detectable HIV RNA and infrequent attendance at the clinic. However, other factors for remaining untreated, such as older age, history of injecting drug use and severe alcohol use, were inconsistent across cohorts. Although the reasons for these inconsistent findings are unclear, they could be in part due to differences in statistical methods, definitions, study populations or health care systems. Given these differences, the results from these studies are difficult to reliably compare. A similar analysis in a large multinational collaboration of cohorts would allow a more robust identification of factors associated with lack of DAA treatment initiation, particularly in relation to differences between regions and health care systems.

The aim of our study was therefore to determine the rate at which individuals with HIV/HCV in six countries remained DAA-untreated over time following unrestricted access to DAA. Additionally, we examined demographic, clinical, and behavioral factors associated with lack of DAA-uptake in the context of universal DAA availability. Finally, the difference in the strength of association for observed factors was evaluated across countries to determine their generalizability and contextual relevance.

METHODS

Study design and setting

This study was a retrospective analysis of prospectively collected data from the International Collaboration on Hepatitis C Elimination in HIV Cohorts (InCHEHC) [ref to follow]. This consortium includes pooled data from 11 observational cohorts of people living with HIV from six countries. For the current analysis, data from nine cohorts from six countries were used (Table 1).

Study population

We included all people living with HIV enrolled in InCHEHC who were known to be HCV RNA-positive following unrestricted DAA access in the country/region of their respective cohort (i.e., last known HCV RNA before unrestricted access to DAA was positive or a recorded HCV RNA positive test after unrestricted access date). Unrestricted access to DAA treatment was defined as the date of lifting all restrictions on access to interferon-free DAA regimens for the treatment of HCV infection in people living with HIV. These restrictions excluded those pertaining to decentralized DAA prescriptions or provider type, as these are still in place in many countries. We excluded individuals without at least one HIV- or HCV-related visit after unrestricted access to DAA, individuals with suspected spontaneous HCV clearance and individuals whose last HCV RNA result before unrestricted access was positive, but had initiated DAA treatment prior to unrestricted access and achieved SVR after the date of unrestricted access. As access to healthcare and reasons to remain DAA-untreated were likely affected by the COVID-19 pandemic, we chose to include all data until February 1, 2020.

Covariables

We collected demographic variables (age, gender, region of origin), HIV-related variables [mode of HIV transmission, HIV RNA, CD4 cell count, antiretroviral therapy (ART) history, number of visits to the HIV outpatient clinic] and liver-related variables (HCV antibody, HCV genotype, HCV RNA, HCV treatment history, liver stiffness measurements, liver-related laboratory tests including transaminases and platelet count). Additionally, for a subset of cohorts, behavioral variables (injecting drug use, number of sexual contacts for MSM, HCV-positive sex partners, condomless sex, group sex) and socioeconomic variables [educational level according to the International Standard Classification of Education (ISCED), housing situation, employment status] were available. Individuals were assigned to a key population based on their mode of HIV and/or HCV transmission. We considered any MSM who ever injected drugs as part of the MSM key population. HIV- or HCV-related visits were defined as visits to the HIV outpatient clinic, cohort-related

Table 1. Cohort profile of the included cohorts in the current analysis

Country	Cohort	InCHEHC participants	Cohort type	Key populations[a]	Date of unrestricted DAA access[b]	Date of limited DAA access	Data updated until
Australia	ACCESS	22.033[c]	Nationwide health surveillance network including PLWH	MSM: 61% PWID: n.a.	2016-03-01	None	2021-07-13[d]
	CEASE	402[c]	Cohort of individuals with HIV/HCV from multiple Australian states.	MSM: 84% PWID: 10%			2018-07-24
Canada	CCC0	2,032	Nationwide cohort of individuals with HIV/HCV	MSM: 23% PWID: 54%	Quebec: 2016-07-01[e] BC & Ontario: 2017-03-01[e]	2013-11-21	2021-06-01[d]
France	Aquitaine	9,296	Cohort of PLWH from 13 sites in South-West France	MSM: 41% PWID: 20%	2014-11-01[f]	2014-01-01	2021-07-13[d]
	HEPAVIH	1.723[c]	Nationwide cohort of individuals with HIV/HCV	MSM: 16% PWID: 63%			2019-11-06
	SAIDCC	7.466[c]	Single centre cohort	MSM: 54% PWID: 5%			2017-12-31
Netherlands	ATHENA	24.785	Nationwide cohort of PLWH	MSM: 61% PWID: 3%	2015-11-01	2014-11-01	2020-02-01
Spain	CORIS	16.725	Nationwide cohort of PLWH	MSM: 77% PWID: 7%	2017-06-01	2015-01-01	2019-12-30
Switzerland	SHCS	20.740	Nationwide cohort of PLWH	MSM: 45% PWID: 19%	2017-11-01	2014-04-01	2020-01-31

[a]MSM with a history of injecting drug use were considered part of the MSM key population. [b]Defined as the date of lifting all restrictions on access to DAAs for treatment of HCV infection in people living with HIV, except for restrictions on decentralized DAA prescriptions. [c]Overlap between ACCESS and CEASE (n=161), overlap between HEPAVIH and SAIDCC (n=98). [d]As access to healthcare and therefore reasons to remain DAA-untreated were affected by the COVID-19 pandemic, we chose to include data until February 1, 2020. [e]Canadian date of unrestricted access varies per province. Due to privacy regulations, province was only known for those living in Quebec, Ontario or British Columbia. [f]In France, individuals with HIV/HCV had unrestricted access to DAA on this date before universal access in the general population.
Abbreviations: HCV: hepatitis C virus. DAA: direct-acting antivirals. PLWH: people living with HIV. MSM: men who have sex with men. PWID: people who inject(ed) drugs. BC: British Columbia

visits, visits at which HIV RNA, HCV RNA, CD4 cell counts, or liver stiffness were measured, or when HCV treatment was initiated or prescribed.

"Definitive" spontaneous clearance was defined as two consecutive undetectable HCV RNA tests, at least 28 days apart, following HCV infection in HCV-untreated individuals. Untreated individuals having only a single undetectable/negative HCV RNA test following HCV infection were classified as having "presumed" spontaneous clearance. Sustained virological response (SVR) was defined as a negative HCV RNA result at least 12 weeks after DAA or DAA + PEG-interferon treatment or 24 weeks after (PEG-)interferon treatment, but prior to the start date of a consecutive antiviral treatment regimen, if any. HCV re-infection was defined as a positive HCV RNA following SVR or definitive spontaneous clearance. Advanced liver fibrosis or cirrhosis was considered to be present if liver stiffness was ≥9.5 kPa or if fibrosis-4 (FIB-4) score was above 2.67.[13]

Statistical analysis

Start of follow-up was defined as: (i) for individuals who were HCV RNA-positive and included in the cohort prior to unrestricted DAA access: the date of unrestricted DAA access for the given country, (ii) for individuals who became HCV RNA-positive after unrestricted DAA access: date of first HCV RNA-positive test result, (iii) for individuals who were HCV RNA-positive at inclusion in the cohort after unrestricted DAA access: the date of inclusion in the cohort. Follow-up continued until DAA treatment initiation or prescription, last HIV- or HCV-related visit, loss to follow-up, moving abroad, cohort exit, or death, whichever occurred first. Included individuals with unsuccessful DAA treatment or re-infection after successful treatment or spontaneous clearance did not recontribute to follow-up.

Individuals were classified as being either DAA-treated or DAA-untreated based on whether or not DAA treatment was initiated following unrestricted access. Demographic and clinical characteristics were summarized using descriptive statistics at DAA treatment initiation for DAA-treated individuals and at the end of follow-up for DAA-untreated individuals, using the most recent value before this moment including data from prior to the follow-up period. If only values after this moment were available, or no values were available at all, the characteristics were considered missing. Additionally, behavioral and socio-economic characteristics were summarized from cohorts with available data.

The primary outcome was the cumulative proportion of individuals who remained DAA-untreated. Time until DAA uptake was summarized using survival curves calculated by the Kaplan-Meier method. These curves were stratified by country. Differences between

the stratified curves were compared for statistical significance using the log-rank test. To identify factors associated with DAA uptake over time, competing-risks regression by means of the Fine-Gray model was used to calculate hazard ratios (HR) and 95% confidence intervals (CI) comparing the rates of initiating DAA treatment across levels of determinants, with the competing risk being death. To avoid using a particular country as a reference category, DAA-uptake per country was compared to the grand mean using effect coding. Factors included in the analysis were selected based on assumed clinical relevance and availability. All factors included in the unadjusted analysis were included for the multivariable analysis. The final model was selected using backwards stepwise selection excluding variables with a p-value above 0.05 based on the Wald test. To assess whether the country affected the relation between explanatory variables and DAA uptake, interaction terms between country and each variable included in the final model were added to the multivariable model, separately. A p-value <0.05 based on the Wald test for the interaction term was considered to be significant interaction. The analysis on determinants was additionally stratified for the key populations MSM and people who inject(ed) drugs (PWID). As a sensitivity analysis, we reanalyzed the data while basing the start of follow-up at the date of first official limited access to DAA per country and not universal access to DAA. This analysis aimed to assess whether differences in rate of DAA initiation between countries might be explained by treatment initiation during the limited DAA access period. Data were analyzed using R (version 4.1.2, Vienna, Austria).

RESULTS

The date of unrestricted access to DAA treatment for people living with HIV ranged from November 1, 2014 in France to November 1, 2017 in Switzerland (Table 1). In total, 104,702 people living with HIV from Australia, Canada, France, the Netherlands, Spain or Switzerland participating in the InCHEHC cohort were assessed for eligibility (Supplementary Figure 1). Of these, 17,983 (17%) ever had a positive HCV antibody, RNA or genotype result. Finally, 4,552 individuals were HCV RNA positive at the time of or after unrestricted access to DAA and were thus included in the analysis. Median follow-up duration was 7.3 months (IQR 2.3 – 19.5). The majority of included individuals was followed in France (*n*=1,069; 23%), the Netherlands (*n*=1,044; 23%) and Australia (*n*=930; 20%). Most individuals belonged to the MSM (*n*=2,156; 47%) or PWID (*n*=1,453; 32%) key population. Advanced fibrosis or cirrhosis was present in 901/3,809 (24%) of included individuals with available data.

In total, 3,187/4,552 (70%) of the included individuals initiated DAA treatment during follow-up. Population characteristics of DAA-treated and DAA untreated individuals are described in Table 2. Median time from inclusion to DAA initiation was 5 months (IQR: 2 – 12). As shown in Figure 1, time until DAA initiation differed significantly between the six different countries (log-rank test $p<0.0001$).Among DAA-treated individuals, median number of months from inclusion to DAA initiation per country was 3 (IQR: 1 – 7) for Australia, 4 (IQR: 2 – 8) for the Netherlands, 5 (2 – 10) for Switzerland, 6 (IQR: 2 – 13) for Canada, 7 (3 – 13) for Spain, and 10 (IQR: 1 – 18) for France.

Table 2. Characteristics of participants by DAA treatment status

	DAA-untreated (n=1365)	DAA-treated (n=3187)
Male sex	1075 (79%)	2651 (83%)
Age (median, IQR)	51 (44 – 57)	51 (44 – 55)
HIV key population[a]		
MSM	536 (39%)	1620 (51%)
PWID	478 (35%)	975 (31%)
Heterosexual	149 (11%)	242 (8%)
Other/unknown	202 (15%)	350 (11%)
Country		
Australia	285 (21%)	645 (20%)
Canada	151 (11%)	308 (10%)
France	194 (14%)	875 (27%)
The Netherlands	156 (11%)	888 (28%)
Spain	333 (24%)	276 (9%)
Switzerland	246 (18%)	195 (6%)
Ever prescribed ART	1107 (81%)	2810 (88%)
HIV RNA		
Undetectable[b]	959 (70%)	2646 (83%)
Detectable	261 (19%)	315 (10%)
Missing	145 (11%)	226 (75)
CD4 count (median, IQR)	617 (360 – 825)	633 (451 – 848)
Ever diagnosed with AIDS	287 (21%)	565 (18%)
Ever treated for HCV prior to unrestricted DAA access	294 (22%)	794 (25%)
Years since first positive HCV test (median, IQR)	8 (3 – 14)	6 (1 – 13)
HCV re-infection	82 (6%)	200 (6%)
Most recent Fibroscan® result		
F0-F2 (<9.5 kPa)	380 (28%)	993 (31%)
F3-F4 (≥9.5 kPa)	107 (8%)	276 (9%)
Missing	878 (64%)	1918 (60%)
FIB-4 score		
<2.67	786 (58%)	1603 (50%)
≥2.67	219 (16%)	385 (12%)
Missing	360 (26%)	1199 (38%)

Data are reported as number (percentage) unless otherwise noted. Characteristics were summarized at the start of DAA therapy for DAA-treated individuals and at the most recent outpatient clinic visit for DAA-untreated individuals. [a]The ACCESS cohort includes data on sexual orientation but not on HIV or HCV transmission route. Therefore, HIV key population for ACCESS participants is classified as either MSM or other/unknown. [b]Defined as <=50 copies/ml or below the detection limit of the used assay.
Abbreviations: DAA: direct-acting antivirals. IQR: interquartile range. MSM: men who have sex with men. PWID: people who inject(ed) drugs. HCV: hepatitis C virus. c-ART: combined antiretroviral therapy.

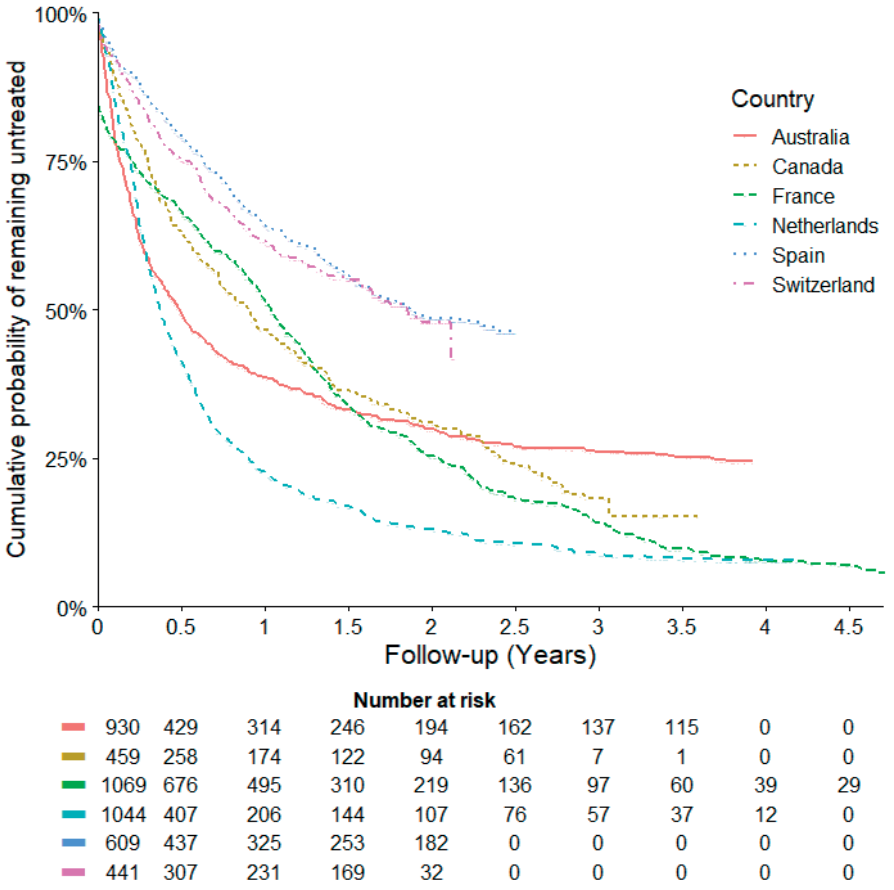

Figure 1. DAA treatment initiation per country following unrestricted access
Data from InCHEHC collaboration including the following cohorts: CEASE (Australia), CCC0 (Canada), HEPAVIH (France), SAIDCC (France), ATHENA (the Netherlands), CORIS (Spain), SHCS (Switzerland). Log-rank test: $p<0.0001$. Abbreviations: DAA: direct-acting antivirals.

In multivariable analysis (Table 3), factors associated with an increased rate of DAA initiation during universal access were being linked to care in Australia, France, or the Netherlands, ever having been prescribed ART, having a higher CD4 count, and ever having been treated for HCV prior to unrestricted access to DAA. Compared to belonging to the MSM key population, being a male heterosexual or a female with an HIV transmission route classified other than heterosexual transmission or injecting drug use, or an unknown HIV transmission route, were associated with a lower rate of DAA treatment initiation. Additionally, longer duration since the first positive HCV test, detectable or missing HIV RNA status and missing non-invasive parameters of liver

Table 3. Factors associated with rate of DAA initiation

	Univariable		Multivariable[a]	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Age, per 10 years	0.95 (0.91 – 0.98)	0.002		
Gender/HIV key population				
MSM	Ref		Ref	
PWID, male	0.70 (0.64 – 0.77)	<0.001	0.93 (0.83 – 1.03)	0.16
PWID, female	0.69 (0.61 – 0.77)	<0.001	0.95 (0.83 – 1.09)	0.46
Heterosexual, male	0.60 (0.50 – 0.73)	<0.001	0.69 (0.56 – 0.84)	<0.001
Heterosexual, female	0.64 (0.54 – 0.76)	<0.001	0.86 (0.73 – 1.02)	0.09
Other/unknown, male	0.72 (0.63 – 0.82)	<0.001	0.89 (0.77 – 1.03)	0.11
Other/unknown, female	0.66 (0.53 – 0.81)	<0.001	0.74 (0.58 – 0.93)	0.01
Country[b]				
Australia	1.25 (1.15 – 1.36)	<0.001	1.67 (1.46 – 1.92)	<0.001
Canada	1.02 (0.92 – 1.12)	0.75	0.91 (0.82 – 1.02)	0.09
France	1.34 (1.26 – 1.43)	<0.001	1.42 (1.31 – 1.54)	<0.001
the Netherlands	1.82 (1.69 – 1.94)	<0.001	1.54 (1.43 – 1.66)	<0.001
Spain	0.57 (0.51 – 0.63)	<0.001	0.48 (0.43 – 0.54)	<0.001
Switzerland	0.57 (0.50 – 0.65)	<0.001	0.63 (0.54 – 0.73)	<0.001
Ever prescribed c-ART versus never	1.55 (1.40 – 1.71)	<0.001	1.17 (1.05 – 1.31)	0.005
HIV RNA status				
Undetectable (<50 copies/ml)	Ref		Ref	
Detectable	0.61 (0.54 – 0.69)	<0.001	0.64 (0.57 – 0.73)	<0.001
Missing	0.75 (0.65 – 0.86)	<0.001	0.59 (0.48 – 0.72)	<0.001
CD4 count, square root	1.01 (1.01 – 1.02)	0.001	1.01 (1.00 – 1.01)	0.004
Ever diagnosed with AIDS versus never diagnosed with AIDS	0.84 (0.77 – 0.92)	<0.001		
Ever treated for HCV before unrestricted DAA access versus never HCV-treated	1.13 (1.04 – 1.22)	0.004	1.23 (1.12 – 1.34)	<0.001
HCV re-infection versus primary infection	1.07 (0.93 – 1.24)	0.33		
Years since first positive HCV test, per year	0.98 (0.97 – 0.98)	<0.001	0.97 (0.96 – 0.98)	<0.001
Liver fibrosis stage[c]				
No advanced fibrosis	Ref		Ref	
Advanced fibrosis/cirrhosis	0.92 (0.84 – 1.00)	0.06	0.97 (0.88 – 1.07)	0.5
Missing	0.91 (0.82 – 1.01)	0.08	0.77 (0.64 – 0.92)	0.005

Parameter estimates obtained from competing-risks regression analysis using the Fine-Gray method. [a]The final model was build using stepwise backwards selection. Initially, all variables analyzed in the univariable analysis were included. Then, the variable with the highest p-value was removed from the model until all remaining variables had a p-value <0.05. [b]To avoid using a particular country as a reference category, DAA-uptake per country was compared to the grand mean using effect coding. [c]Advanced fibrosis or cirrhosis defined as Fibroscan value (≥9.5 kPa) or FIB-4 (≥2.67).

Abbreviations: DAA: direct-acting antiviral. HR: hazard ratio. CI: confidence interval. MSM: men who have sex with men. PWID: people who inject(ed) drugs. C-ART: combined antiretroviral therapy. AIDS: Acquired Immunodeficiency Syndrome. HCV: hepatitis C virus.

Table 4. Factors associated with rate of DAA treatment initiation for MSM and PWID

	MSM (n=2156)		PWID (n=1453)	
	HR (95% CI)[a]	**P-value**	**HR (95% CI)[a]**	**P-value**
Age, per 10 years			0.85 (0.77 – 0.93)	<0.001
Female versus male sex	n.a.			
Country[b]				
Australia	1.83 (1.57 – 2.13)	<0.001	2.25 (1.53 – 3.32)	<0.001
Canada	0.98 (0.81 – 1.19)	0.8	0.98 (0.81 – 1.17)	0.8
France	1.22 (1.07 – 1.39)	0.004	1.55 (1.35 – 1.77)	<0.001
the Netherlands	1.71 (1.55 – 1.88)	<0.001	1.08 (0.91 – 1.28)	0.4
Spain	0.54 (0.46 – 0.62)	<0.001	0.41 (0.34 – 0.51)	<0.001
Switzerland	0.50 (0.40 – 0.63)	<0.001	0.67 (0.52 – 0.85)	<0.001
Ever c-ART prescribed versus never c-ART			1.23 (1.05 – 1.45)	0.01
HIV RNA status				
Undetectable (<50 copies/ml)	Ref		Ref	
Detectable	0.76 (0.64 – 0.91)	0.002	0.53 (0.41 – 0.67)	<0.001
Missing	0.64 (0.52 – 0.79)	<0.001	2.34 (1.79 – 3.05)	<0.001
CD4 count, square root			1.01 (1.00 – 1.02)	0.03
Ever diagnosed with AIDS versus never diagnosed with AIDS				
Ever treated for HCV before unrestricted DAA access versus never HCV-treated	1.38 (1.22 – 1.57)	<0.001		
HCV re-infection versus primary infection				
Years since first positive HCV test, per year	0.94 (0.93 – 0.96)	<0.001	0.99 (0.98 – 1.00)	0.01
Liver fibrosis stage[c]				
No advanced fibrosis	Ref	Ref	Ref	Ref
Advanced fibrosis/cirrhosis	0.94 (0.80 – 1.10)	0.4	1.11 (0.96 – 1.29)	0.1
Missing	0.67 (0.55 – 0.82)	<0.001	2.06 (1.13 – 3.73)	0.02

Parameter estimates obtained from a competing-risks regression analysis using the Fine-Gray method. [a]Only the results of the multivariable analyses are displayed. Supplementary table 5 displays both univariable and multivariable hazard ratios. The final model was build using stepwise backwards selection. Initially, all variables that are listed were included, except for male versus female sex that was not included in the MSM sub-analysis. Then, the variable with the highest p-value was removed from the model until all remaining variables had a p-value <0.05. [b]To avoid using a particular country as a reference category, DAA-uptake per country was compared to the grand mean using effect coding. [c]Advanced fibrosis or cirrhosis defined as Fibroscan value (≥9.5 kPa) or FIB-4 (≥2.67).
Abbreviations: DAA: direct-acting antivirals. MSM: men who have sex with men. PWID: people who inject(ed) drugs. HR: hazard ratio. CI: confidence interval. C-ART: combined antiretroviral therapy. AIDS: Acquired Immunodeficiency Syndrome. HCV: hepatitis C virus.

fibrosis were associated with a lower rate of DAA initiation. There was evidence that the association between receiving HCV treatment before unrestricted access to DAA or liver fibrosis stage and rates of DAA initiation were different across countries (*p* for interaction<0.001 for both).

Before universal DAA access, several countries had limited access to DAA treatment, with the date of its implementation ranging from November 21, 2013 in Canada to January 1, 2015 in Spain (Table 1). Australia never had a period of limited access, thus access date was taken as the primary analysis for Australia. In the sensitivity analysis basing the start of follow-up on the date of limited access to DAA, 6,416 individuals were included (Supplementary figure 2). Median follow-up duration was 17.1 months (IQR: 5.0 – 32.0). In total, 4,730 (74%) initiated DAA treatment after median 15 months (IQR: 4 - 27) of follow-up (Supplementary table 1). During follow-up in this analysis, the rate of DAA initiation varied significantly between countries (Supplementary figure 3, *p*<0.0001), yet the cumulative proportion remaining DAA-untreated by the end of follow-up was similar between countries. In multivariable analysis, factors associated with the rate of DAA initiation were similar to the analyses basing the start of follow-up on the date of unrestricted access to DAA (Supplementary table 2). The main differences between analyses were that belonging to the PWID key population was significantly associated with a lower rate of DAA initiation and that having advanced liver fibrosis or cirrhosis was significantly associated with a higher rate of DAA initiation from limited access.

In total 1,839 DAA-treated and 876 DAA-untreated individuals were included in six cohorts with available behavioral data (Supplementary table 3). Risk behaviors associated with HCV transmission, such as injecting drug use, needle or syringe sharing and condomless sex, were common to both the DAA-treated and DAA-untreated groups. Educational level and housing situation were also no different between both groups.

Time until DAA initiation differed significantly between key populations (Supplementary Figure 4, log-rank test *p*<0.0001). In total, 1,620 of the 2,156 (75%) included MSM and 975 of the 1,453 (67%) included PWID initiated DAA treatment during follow-up (Supplementary table 4). Median time from inclusion to DAA initiation was 4 months (IQR: 1 - 8) for MSM and 8 months (IQR: 2 - 17) for PWID (Mood's Median Test: *p*<0.001). In stratified competing-risk regression, characteristics associated with higher rates of DAA initiation in both key populations were country (i.e. Australia, France), undetectable HIV RNA status, and lower number of years since the first positive HCV test (Table 5). Having received HCV treatment prior to unrestricted access to DAA was associated with a higher rate of DAA initiation among MSM only, whereas younger age and higher CD4 counts were associated with higher rates of DAA initiation among PWID only. Regarding

country, the Netherlands was the only country that had a significantly higher rate of DAA treatment initiation in one key population (i.e., MSM), but not significantly higher in another (i.e., PWID).

DISCUSSION

The advent of highly effective DAA therapy has resulted in a global effort to pursue HCV micro-elimination among people living with HIV. In this unique, multinational study we assessed factors associated with the rate of DAA initiation following unrestricted access among individuals with HIV/HCV in several high-income countries. Despite DAA agents being available with universal access for several years (range 2 – 5 years), 30% of HCV-viremic individuals with HIV included in this study remained DAA-untreated during follow-up. Significant differences in rates of DAA-uptake were observed between countries, indicating potential differences in access to care and barriers to treatment. Furthermore, several factors associated with rates of DAA initiation were found, with partially different risk profiles for untreated PWID and MSM. We provide information that helps to understand the untreated, which could allow physicians engaged in HIV care to enhance DAA-uptake and guide future strategies to further optimize care for this population.

Several indicators of engagement in HIV care and HIV treatment adherence were independently associated with a lower rate of DAA treatment initiation, including having a detectable HIV RNA level and a lower CD4 count. Additionally, lower rates of DAA initiation were observed in individuals with missing HIV RNA or missing data on liver fibrosis parameters, which could also be considered proxies for lower engagement in care. Hence, these results indicate an overlap between groups receiving sub-optimal care for both HIV and HCV and are in line with two previous studies that reported an association between lower frequency of visits and lack of DAA-uptake.[9,11] As untreated HIV infection is associated with an accelerated progression of liver fibrosis in individuals with HIV/HCV,[14] both HIV and HCV treatment of co-infected individuals are of particular importance.

We demonstrated considerable variation between key populations regarding the rate of DAA initiation. Compared to MSM, all other key populations had a lower rate of DAA initiation. Additionally, for DAA-treated individuals median time from inclusion to DAA treatment was significantly longer in PWID than in MSM. This might indicate differences in access to healthcare between key populations. However, in multivariable analysis with follow-up starting from unrestricted access, statistical significance was only observed for males with heterosexual HIV transmission and females with a route of HIV transmission other than injecting drug use or heterosexual, or an unknown route of HIV transmission. Of note, in the ACCESS cohort, accounting for 74% of inclusions from Australia, participants could not be assigned to the PWID or heterosexual key populations due to lacking data on HIV or HCV transmission route. As Australia was the

country with the highest rate of DAA initiation, this might have impacted the analysis on differences between key populations. Furthermore, differences between key populations were harder to assess than other variables, since cohorts might use different definitions for assignment to HIV key populations, e.g. MSM with a history of injecting drug use can be variably assigned to the MSM or PWID key population.

Rates in DAA-uptake also varied across countries. Some of these differences could be explained by differing health care systems and when DAA restrictions were lifted. The two countries (i.e., Switzerland and Spain) with a significantly lower rate of DAA initiation, compared to the population mean, both had a more gradual lifting of treatment restrictions and a later introduction of unrestricted access to DAA. Consequently, a larger proportion of individuals with HIV/HCV in these countries was treated before unrestricted access[15,16] and the HCV-viremic population during unrestricted access to DAA might have been a selection of individuals less likely to initiate treatment. As an example, in Switzerland many MSM with HIV/HCV were treated in a trial that finished before unrestricted access to DAA was granted.[17] This explanation is supported by the fact that the differences among countries became smaller when the rate of DAA initiation was analyzed while basing inclusion on the moment of official limited access to DAA. However, between-country differences remained. Additionally, variation in HCV testing rates between countries could impact variation in time to DAA initiation. Furthermore, differences could have been caused by the nature of time-to-event analysis and violation of the proportional hazards assumption, with treatment uptake shortly after start of follow-up having a greater impact on hazard ratios (p for interaction between country and follow-up time <0.001). In the countries with early unrestricted access, HCV treatment uptake peaked very quick, compared to the more gradual uptake in countries with a stepwise release of restrictions (Supplementary figure 5).

Despite country differences in rate of DAA initiation, a considerable proportion of HCV-viremic individuals have received treatment in all settings. Moreover, when basing inclusion on the moment of official limited access to DAA treatment, the proportion of HCV-viremic individuals that had initiated DAA treatment at the end of follow-up was rather similar between the countries assessed. These successes do help bring each country towards micro-elimination; however, they must be weighed with potential obstacles. As observed in this study, a substantial proportion of DAA-untreated individuals reported behavior associated with the risk of onward HCV transmission, such as injecting drug use and condomless sex. The lack of DAA-uptake could potentially serve as a driving factor for onward circulation of HCV. This issue does not seem to be confined within a specific country,[9] considering that some settings have shown an increase in the proportion of external introductions of HCV infections due to international transmission

among MSM.[18] Thus, reducing incidence of primary HCV infections and HCV re-infections and thereby progress towards HCV micro-elimination requires an increase in DAA-uptake across all countries.

For policy makers, it is important to compare HCV elimination results between countries or regions, as these differences could highlight HCV elimination strategies that were successful in other countries and perhaps could be applicable to their own setting. For example, the country with the highest rate of DAA initiation following unrestricted access (i.e., Australia) has had many successful examples of decentralized DAA care pathways[19–21] that are currently uncommon to most European countries. As our results indicated that several proxies for lower engagement in care were associated with a lower rate of DAA initiation, it can be argued that reducing the threshold for DAA-uptake through decentralized DAA care pathways might be a valuable tool for HCV micro-elimination. The feasibility, benefit and (cost-)effectiveness of decentralized DAA access has been demonstrated by multiple studies, mainly including PWID.[22–26]

Our analysis of a large-scale, intercontinental collaboration of cohorts allowed us to compare DAA-uptake across several countries and health-care systems, while identifying factors associated with a lower rate of DAA initiation that are not necessarily country-specific. Nevertheless, there are several limitations of this study. First, a positive HCV RNA test was required for inclusion and individuals who tested HCV antibody positive with missing HCV RNA status were not included. This selection criterion might have biased the proportion of individuals remaining DAA-untreated. Furthermore, excluding individuals with presumed spontaneous HCV clearance based on only one negative HCV RNA result might have resulted in incorrectly excluding individuals who did not achieve definitive spontaneous clearance. Of the 764 individuals excluded because of presumed spontaneous clearance, 65 (9%) had a subsequent HCV RNA-positive test, which could either be due to reinfection or incorrect classification of spontaneous clearance. Importantly, this percentage is in line with the proportion of re-infections following spontaneous clearance reported in literature,[6,27] and therefore the effect of this potential misclassification bias is likely minimal. Third, due to a lack of data or inconsistencies in reporting data between cohorts, several characteristics known to be associated with poor DAA-uptake were not accounted for in the analysis and included socioeconomic characteristics and frequency of outpatient clinic visits[9,11].

In conclusion, of the countries included in this international cohort, there remains a substantial group of HCV-viremic people living with HIV who have yet to initiate DAA treatment despite universal access to DAA. As these individuals likely contribute to ongoing national and international HCV transmission and are at risk of HCV-related

mortality, treating this population may be a critical step towards achieving HCV elimination. Efforts to increase engagement in care as well as decentralized DAA care pathways are required to increase DAA-uptake among the remaining group of HCV-viremic people with HIV.

Declaration of interest

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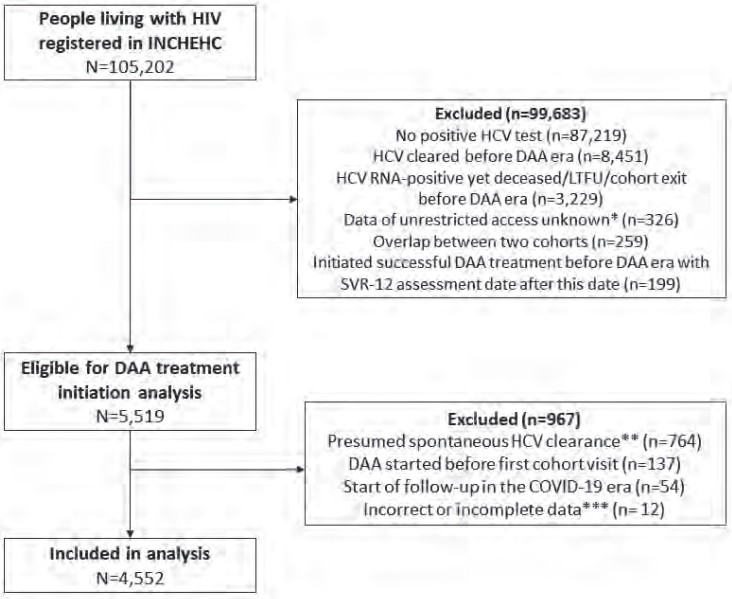
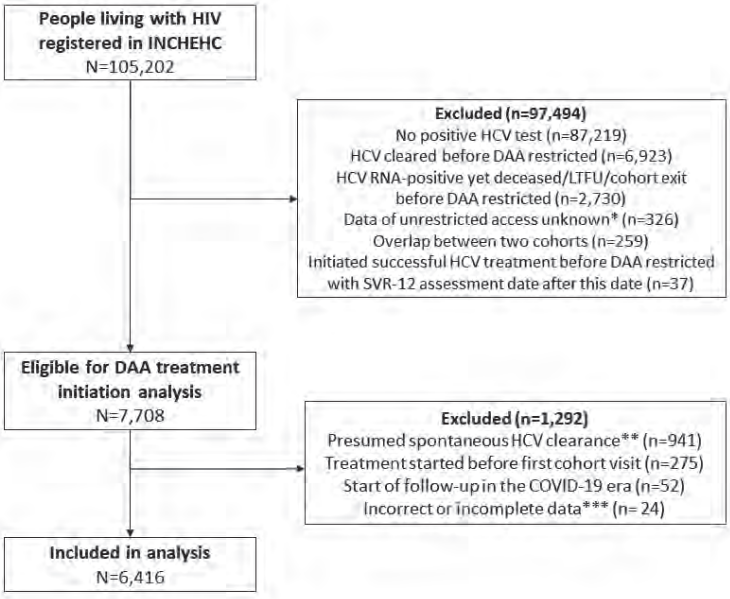
SUPPLEMENTARY MATERIAL

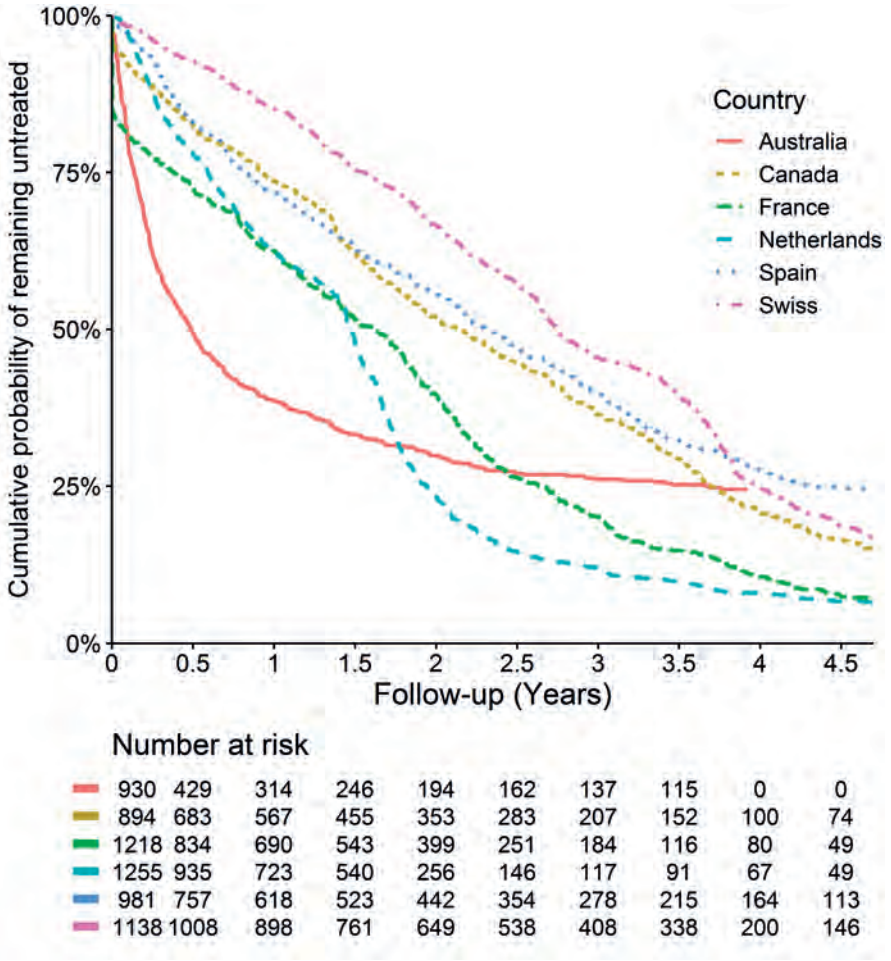


Supplementary figure 1. Flowchart for the selection of individuals included in the analysis of DAA-treatment uptake

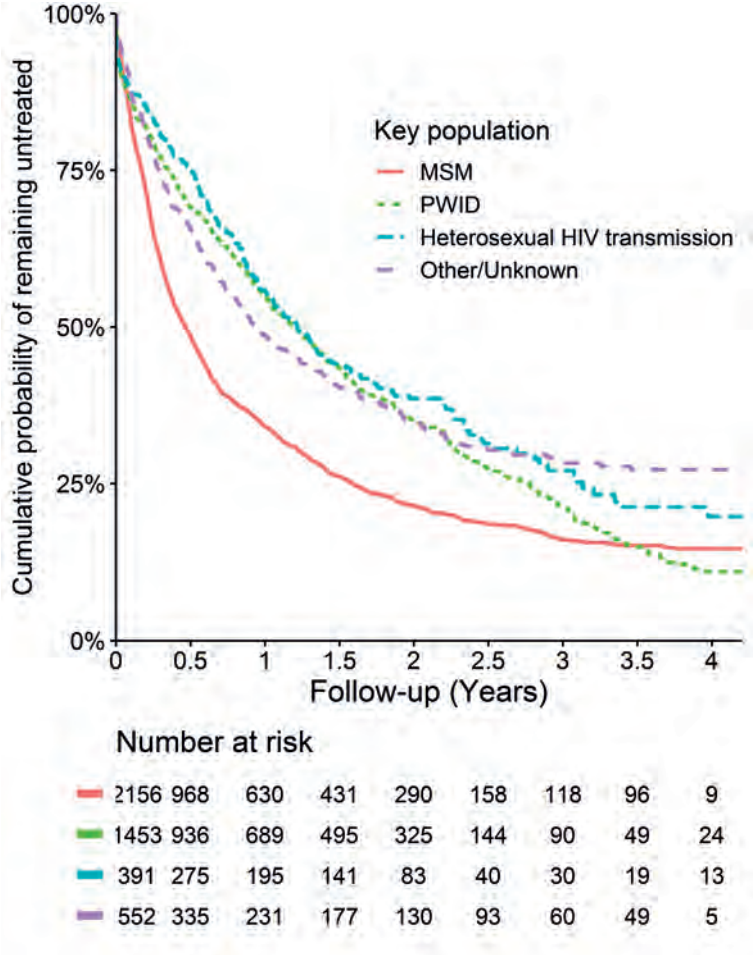
*Canadian date of unrestricted access varies per province. Due to privacy regulations, province was only known for those living in Quebec, Ontario or British Columbia and therefore participants from other Canadian provinces were excluded. **Untreated patients having only a single undetectable/negative HCV RNA test following HCV infection were classified as having "presumed" spontaneous clearance. ***Negative FU of more than one month (i.e. incorrect date of positive HCV RNA test or incorrect date of DAA initiation). Abbreviations: HCV: hepatitis C virus. DAA: direct-acting antivirals. SVR: sustained virological response.



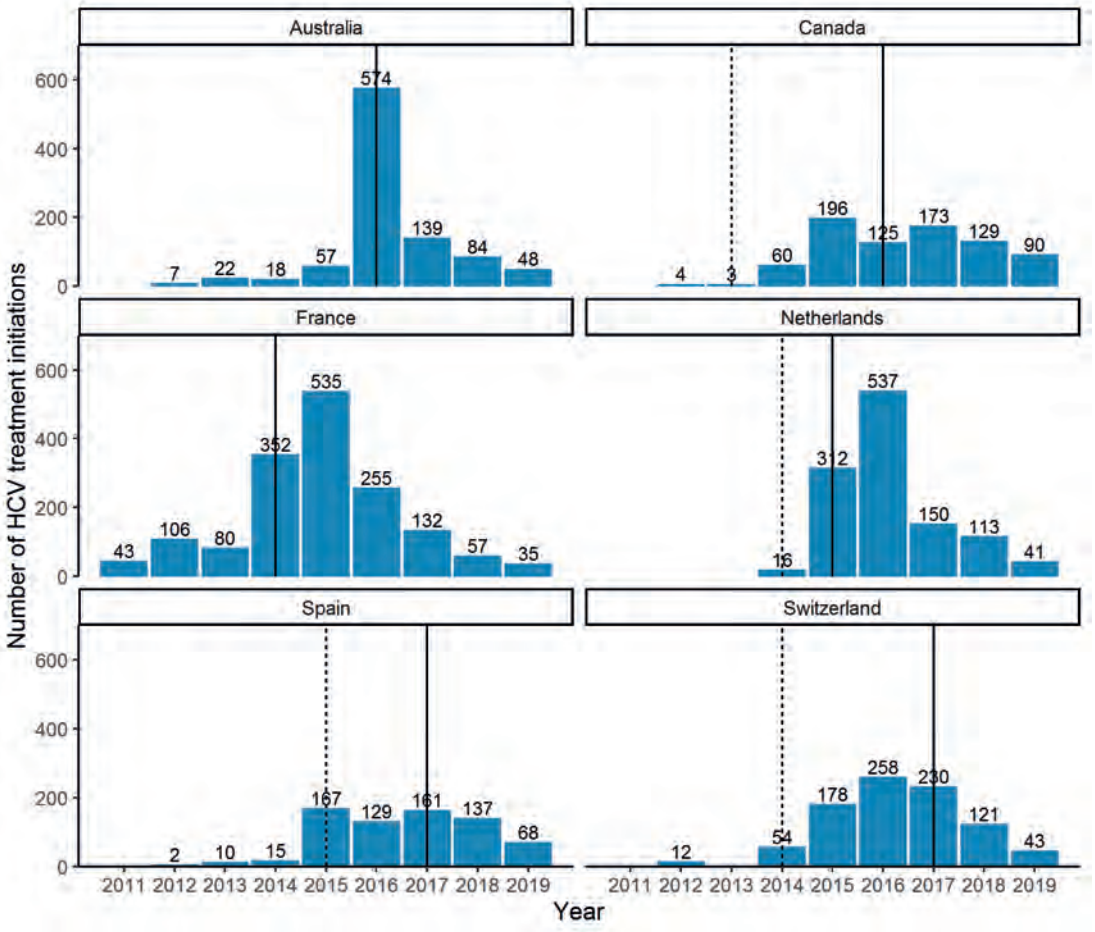
Supplementary figure 2. Flowchart for the selection of individuals included in the analysis of DAA-treatment uptake basing inclusion on the date of official limited access to DAA
*Canadian date of access varies per province. Due to privacy regulations, province was only known for those living in Quebec, Ontario or British Columbia and therefore participants from other Canadian provinces were excluded. **Untreated patients having only a single undetectable/negative HCV RNA test following HCV infection were classified as having "presumed" spontaneous clearance. ***Negative FU of more than one month (i.e. incorrect date of positive HCV RNA test or incorrect date of DAA initiation). Abbreviations: HCV: hepatitis C virus. DAA: direct-acting antivirals. SVR: sustained virological response.



Supplementary figure 3. DAA treatment initiation per country following official limited access to DAA Data from InCHEHC collaboration including the following cohorts: CEASE (Australia), CCC0 (Canada), HEPAVIH (France), SAIDCC (France), ATHENA (the Netherlands), CORIS (Spain), SHCS (Switzerland). Log-rank test: $p<0.0001$. Abbreviations: DAA: direct-acting antivirals.



Supplementary Figure 4. DAA treatment initiation per key population following unrestricted access Data from InCHEHC collaboration including the following cohorts: CEASE (Australia), CCC0 (Canada), HEPAVIH (France), SAIDCC (France), ATHENA (the Netherlands), CORIS (Spain), SHCS (Switzerland). Log-rank test: $p<0.0001$. Abbreviations: DAA: direct-acting antivirals.



Supplementary figure 5. Absolute number of DAA-containing Hepatitis C virus treatment initiations per country between 2011 and 2019

Dashed vertical line represents the year of limited access. Solid vertical line represents the year of unrestricted access. Exact dates are given in table 1. Data includes all HCV treatment regimens that include DAA, both with and without PEG-interferon and ribavirin. Boceprevir and telaprevir are excluded from the analysis. Two treatment initiations occurring on the same start date within a participant (e.g. once sofosbuvir and once ledipasvir) were only counted once. Abbreviations: DAA: direct-acting antivirals. HCV: hepatitis C virus.

Supplementary table 1. Characteristics of participants by DAA treatment status, basing inclusion on the date of official limited access to DAA.

	DAA-untreated (n=1,686)	DAA-treated (n=4,730)
Male sex	1302 (77%)	3869 (82%)
Age (median, IQR)	50 (43 – 57)	51 (44 – 55)
HIV key population[a]		
MSM	614 (36%)	2217 (47%)
PWID	657 (39%)	1641 (35%)
Heterosexual	177 (10%)	396 (8%)
Other/unknown	238 (14%)	476 (10%)
Country		
Australia	285 (17%)	645 (14%)
Canada	289 (17%)	605 (13%)
France	230 (14%)	988 (21%)
The Netherlands	197 (12%)	1058 (22%)
Spain	368 (22%)	613 (13%)
Switzerland	317 (19%)	821 (17%)
Ever c-ART prescribed	1341 (79%)	3879 (82%)
HIV RNA status		
Undetectable[b]	1191 (71%)	4075 (86%)
Detectable	340 (20%)	424 (9%)
Missing	155 (9%)	231 (5%)
CD4 count (median, IQR)	545 (333 – 788)	610 (430 – 830)
Ever diagnosed with AIDS	379 (22%)	956 (20%)
Ever treated for HCV prior to unrestricted DAA access	224 (13%)	1152 (24%)
Years since first positive HCV test (median, IQR)	7 (3 – 13)	7 (2 – 14)
HCV re-infection	59 (3%)	228 (5%)
Most recent Fibroscan® result		
F0-F2 (<9.5 kPa)	445 (26%)	1607 (34%)
F3-F4 (≥9.5 kPa)	136 (8%)	716 (15%)
Missing	1105 (66%)	2407 (51%)
FIB-4 score		
<2.67	946 (56%)	2586 (55%)
≥2.67	352 (21%)	822 (17%)
Missing	388 (23%)	1322 (28%)

Data are reported as number (percentage) unless otherwise noted. Characteristics were summarized at the start of DAA therapy for DAA-treated individuals and at the most recent outpatient clinic visit for DAA-untreated individuals. [a]The ACCESS cohort includes data on sexual orientation but not on HIV or HCV transmission route. Therefore, HIV key population for ACCESS participants is classified as either MSM or other/unknown. [b]Defined as <=50 copies/ml or below the detection limit of the used assay.

Abbreviations: DAA: direct-acting antivirals. IQR: interquartile range. MSM: men who have sex with men. PWID: people who inject(ed) drugs. HCV: hepatitis C virus. c-ART: combined antiretroviral therapy.

Supplementary table 2. Factors associated with rate of DAA initiation in competing-risks regression, basing inclusion on the date of official limited and official unrestricted access to DAA

	Multivariable From limited access		Multivariable From unrestricted access	
	HR (95% CI)[a]	**P-value**	**HR (95% CI)[a]**	**P-value**
Age, per 10 years				
Gender/HIV key population				
MSM	Ref		Ref	
PWID, male	0.91 (0.83 – 0.99)	0.03	0.93 (0.83 – 1.03)	0.16
PWID, female	0.88 (0.79 – 0.97)	0.01	0.95 (0.83 – 1.09)	0.46
Heterosexual, male	0.70 (0.60 – 0.82)	<0.001	0.69 (0.56 – 0.84)	<0.001
Heterosexual, female	0.80 (0.70 – 0.92)	<0.001	0.86 (0.73 – 1.02)	0.09
Other/unknown, male	0.91 (0.80 – 1.04)	0.2	0.89 (0.77 – 1.03)	0.11
Other/unknown, female	0.73 (0.60 – 0.89)	0.002	0.74 (0.58 – 0.93)	0.01
Country[b]				
Australia	1.85 (1.56 – 2.20)	<0.001	1.67 (1.46 – 1.92)	<0.001
Canada	0.70 (0.64 – 0.76)	<0.001	0.91 (0.82 – 1.02)	0.09
France	1.27 (1.17 – 1.37)	<0.001	1.42 (1.31 – 1.54)	<0.001
the Netherlands	1.16 (1.09 – 1.24)	<0.001	1.54 (1.43 – 1.66)	<0.001
Spain	0.63 (0.58 – 0.68)	<0.001	0.48 (0.43 – 0.54)	<0.001
Switzerland	0.84 (0.77 – 0.90)	<0.001	0.63 (0.54 – 0.73)	<0.001
Ever c-ART prescribed versus never c-ART	1.14 (1.04 – 1.24)	0.003	1.19 (1.06 – 1.33)	0.003
HIV RNA status				
Undetectable (<50 copies/ml)	Ref		Ref	
Detectable	0.59 (0.52 – 0.66)	<0.001	0.64 (0.57 – 0.73)	<0.001
Missing	0.51 (0.40 – 0.65)	<0.001	0.59 (0.48 – 0.72)	<0.001
CD4 count, square root	1.01 (1.00 – 1.01)	0.001	1.01 (1.00 – 1.01)	0.004
Ever diagnosed with AIDS versus never diagnosed with AIDS				
Ever treated for HCV before DAA access versus never HCV-treated	1.45 (1.35 – 1.56)	<0.001	1.23 (1.12 – 1.34)	<0.001
HCV re-infection versus primary infection				
Years since first positive HCV test, per year	0.97 (0.96 – 0.97)	<0.001	0.97 (0.96 – 0.98)	<0.001
Liver fibrosis stage[c]				
No advanced fibrosis	Ref		Ref	
Advanced fibrosis/cirrhosis	1.20 (1.11 - 1.29)	<0.001	0.97 (0.88 – 1.07)	0.5
Missing	0.79 (0.63 – 0.99)	0.04	0.77 (0.64 – 0.92)	0.005

Parameter estimates obtained from competing-risks regression analysis using the Fine-Gray method. [a]The final model was build using stepwise backwards selection. Initially, all variables that are listed were included. Then, the variable with the highest p-value was removed from the model until all remaining variables had a p-value <0.05. [b]To avoid using a particular country as a reference category, DAA-uptake per country was compared to the grand mean using effect coding. [c]Advanced fibrosis or cirrhosis defined as Fibroscan value (≥9.5 kPa) or FIB-4 (≥2.67). Characteristics were summarized at the start of DAA therapy for DAA-treated individuals and at the most recent outpatient clinic visit for DAA-untreated individuals.

Abbreviations: DAA: direct-acting antiviral. HR: hazard ratio. CI: confidence interval. MSM: men who have sex with men. PWID: people who inject(ed) drugs. C-ART: combined antiretroviral therapy. AIDS: Acquired Immunodeficiency Syndrome. HCV: hepatitis C virus.

Supplementary table 3. Behavioral and socioeconomic characteristics of subset of DAA-untreated participants with available behavioral data in six cohorts

	DAA-untreated (n=876)	DAA-treated (n=1,839)
Behavioral		
Injecting drug use		
Ever	137/379 (36%)	516/1,119 (46%)
Past twelve months	118/604 (20%)	263/1,061 (25%)
Needle/syringe sharing past twelve months	5/35 (14%)	9/127 (7%)
MSM sexual partner last twelve months	47/101 (47%)	210/398 (53%)
Recent known HCV-positive sex partner	24/59 (41%)	65/152 (43%)
Recent condomless sex	135/164 (82%)	256/380 (67%)
Group sex[a]	5/8 (63%)	62/132 (47%)
Socioeconomic		
Education level[b]		
Primary education	131 (15%)	285 (15%)
Secondary education	222 (25%)	372 (20%)
Post-secondary education	224 (26%)	434 (24%)
Tertiary education	108 (12%)	211 (11%)
Missing	191 (22%)	537 (29%)
Housing situation		
Stable (own home or rental)	292 (33%)	750 (41%)
Unstable (homeless or shelter)	1 (0.1%)	17 (1%)
Prison	6 (1%)	7 (0.4%)
Missing	577 (66%)	1,065 (58%)

Data are reported as number (percentage). Data reported for individuals included in one of the following cohorts: Aquitaine, HepaVih (France), CCC0 (Canada), Cease (Australia), Coris (Spain), SHCS (Switzerland). Characteristics were summarized at the start of DAA therapy for DAA-treated individuals and at the most recent outpatient clinic visit for DAA-untreated individuals. [a]Only available in three cohorts. [b]Based on the International Standard Classification of Education.
Abbreviations: DAA: direct-acting antivirals. MSM: men who have sex with men. HCV: hepatitis C virus.

Supplementary Table 4. Characteristics of included MSM and PWID by DAA treatment status

	MSM (n=2156)		PWID (n=1453)	
	DAA-untreated (n=536)	**DAA-treated (n=1620)**	**DAA-untreated (n=478)**	**DAA-treated (n=975)**
Male sex	536 (100%)	1620 (100%)	332 (69%)	674 (69%)
Age, in years (median, IQR)	48 (40 – 55)	48 (41 – 54)	53 (47 – 58)	52 (49 – 56)
Country				
Australia	172 (32%)	488 (30%)	4 (1%)[a]	23 (2%)[a]
Canada	29 (5%)	78 (5%)	81 (17%)	164 (17%)
France	52 (10%)	209 (13%)	87 (18%)	483 (50%)
The Netherlands	61 (11%)	636 (39%)	52 (11%)	125 (13%)
Spain	135 (25%)	144 (9%)	154 (32%)	100 (8%)
Switzerland	87 (16%)	65 (4%)	100 (21%)	80 (8%)
Ever c-ART prescribed	450 (84%)	1495 (92%)	370 (77%)	798 (82%)
HIV RNA status				
Undetectable[b]	368 (69%)	1323 (82%)	364 (76%)	872 (89%)
Detectable	92 (17%)	158 (10%)	104 (22%)	91 (9%)
Missing	76 (14%)	139 (9%)	10 (2%)	12 (1%)
CD4 count (median, IQR)	615 (436 – 877)	660 (490 – 840)	515 (304 – 760)	590 (407 – 826)
Ever diagnosed with AIDS	76 (14%)	176 (11%)	143 (30%)	255 (26%)
Ever treated for HCV prior to unrestricted DAA access	89 (17%)	364 (22%)	149 (31%)	314 (32%)
Years since first positive HCV test (median, IQR)	5 (2 – 9)	3 (1 – 7)	12 (6 – 18)	14 (7 – 20)
HCV re-infection	36 (7%)	158 (10%)	28 (6%)	29 (3%)
Advanced fibrosis or cirrhosis[c]				
No	320 (60%)	1103 (68%)	313 (65%)	642 (66%)
Yes	70 (13%)	194 (12%)	157 (33%)	312 (32%)
Missing	146 (27%)	323 (20%)	8 (2%)	21 (2%)

Data are reported as number (percentage) unless otherwise noted. Characteristics were summarized at the start of DAA therapy for DAA-treated individuals and at the most recent outpatient clinic visit for DAA-untreated individuals. [a]The ACCESS cohort includes data on sexual orientation but not on HIV or HCV transmission route. Therefore, HIV key population for ACCESS participants is classified as either MSM or other/unknown. [b]Defined as <=50 copies/ml or below the detection limit of the used assay. [c]Advanced fibrosis or cirrhosis defined as Fibroscan value (≥9.5 kPa) or FIB-4 (≥2.67).
Abbreviations: DAA: direct-acting antivirals. IQR: interquartile range. MSM: men who have sex with men. PWID: people who inject(ed) drugs. HCV: hepatitis C virus. c-ART: combined antiretroviral therapy.

Supplementary table 5. Factors associated with rate of DAA treatment initiation for MSM and PWID

	MSM (n=2156)				PWID (n=1453)			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)[a]	P-value	HR (95% CI)[a]	P-value	HR (95% CI)[a]	P-value	HR (95% CI)[a]	P-value
Age, per 10 years	0.96 (0.92 – 1.01)	0.1			0.87 (0.80 – 0.95)	0.001	0.85 (0.77 – 0.93)	<0.001
Female versus male sex	n.a.		n.a.		0.92 (0.81 – 1.06)	0.26		
Country[b]								
Australia	1.19 (1.08 – 1.32)	<0.001	1.83 (1.57 – 2.13)	<0.001	2.71 (1.91 – 3.84)	<0.001	2.25 (1.53 – 3.32)	<0.001
Canada	1.14 (0.94 – 1.38)	0.2	0.98 (0.81 – 1.19)	0.8	1.03 (0.88 – 1.21)	0.7	0.98 (0.81 – 1.17)	0.8
France	1.16 (1.02 – 1.32)	0.02	1.22 (1.07 – 1.39)	0.004	1.19 (1.05 – 1.34)	0.005	1.55 (1.35 – 1.77)	<0.001
the Netherlands	1.91 (1.74 – 2.10)	<0.001	1.71 (1.55 – 1.88)	<0.001	0.91 (0.76 – 1.08)	0.28	1.08 (0.91 – 1.28)	0.4
Spain	0.61 (0.53 – 0.71)	<0.001	0.54 (0.46 – 0.62)	<0.001	0.48 (0.40 – 0.58)	<0.001	0.41 (0.34 – 0.51)	<0.001
Switzerland	0.54 (0.44 – 0.66)	<0.001	0.50 (0.40 – 0.63)	<0.001	0.68 (0.56 – 0.84)	<0.001	0.67 (0.52 – 0.85)	<0.001
Ever c-ART prescribed versus never c-ART	1.57 (1.36 – 1.82)	<0.001			1.35 (1.15 – 1.58)	<0.001	1.23 (1.05 – 1.45)	0.01
HIV RNA status								
Undetectable (<50 copies/ml)	Ref		Ref		Ref		Ref	
Detectable	0.76 (0.65 – 0.90)	0.001	0.76 (0.64 – 0.91)	0.002	0.64 (0.51 – 0.79)	<0.001	0.53 (0.41 – 0.67)	<0.001
Missing	0.65 (0.54 – 0.77)	<0.001	0.64 (0.52 – 0.79)	<0.001	0.87 (0.49 – 1.54)	0.6	2.34 (1.79 – 3.05)	<0.001
CD4 count, square root	1.00 (0.99 – 1.01)	0.61			1.01 (1.00 – 1.02)	0.06	1.01 (1.00 – 1.02)	0.03
Ever AIDS diagnosis versus never AIDS diagnosis	0.84 (0.72 – 0.99)	0.03			1.13 (0.77 – 1.03)	0.1		
Ever HCV-treated before unrestricted DAA access versus never HCV-treated	0.93 (0.92 – 0.94)	<0.001	1.38 (1.22 – 1.57)	<0.001	1.07 (0.95 – 1.22)	0.3		
HCV re-infection versus primary infection	1.20 (1.02 – 1.42)	0.03			0.90 (0.62 – 1.31)	0.59		
Years since first positive HCV test, per year	0.93 (0.92 – 0.94)	<0.001	0.94 (0.93 – 0.96)	<0.001	0.98 (0.98 – 0.99)	<0.001	0.99 (0.98 – 1.00)	0.01
Liver fibrosis stage[c]								
No advanced fibrosis	Ref		Ref	Ref	Ref		Ref	Ref
Advanced fibrosis/cirrhosis	0.94 (0.80 – 1.09)	0.4	0.94 (0.80 – 1.10)	0.4	1.11 (0.97 – 1.28)	0.1	1.11 (0.96 – 1.29)	0.1
Missing	0.76 (0.67 – 0.87)	<0.001	0.67 (0.55 – 0.82)	<0.001	4.24 (2.74 – 6.57)	<0.001	2.06 (1.13 – 3.73)	0.02

Parameter estimates obtained from a competing-risks regression analysis using the Fine-Gray method. [a]The final model was build using stepwise backwards selection. Initially, all variables that are listed were included, except for male versus female sex that was not included in the MSM sub-analysis. Then, the variable with the highest p-value was removed from the model until all remaining variables had a p-value <0.05. [b]To avoid using a particular country as a reference category, DAA-uptake per country was compared to the grand mean using effect coding. [c]Advanced fibrosis or cirrhosis defined as Fibroscan value (≥9.5 kPa) or FIB-4 (≥2.67).

Abbreviations: DAA: direct-acting antivirals. MSM: men who have sex with men. PWID: people who inject(ed) drugs. HR: hazard ratio. CI: confidence interval. C-ART: combined antiretroviral therapy. AIDS: Acquired Immunodeficiency Syndrome. HCV: hepatitis C virus.

CHAPTER 7

LOW RISK OF FAILING DIRECT-ACTING ANTIVIRALS IN PEOPLE WITH HIV/HCV FROM SUB-SAHARAN AFRICA OR SOUTHEASTERN ASIA: A EUROPEAN CROSS-SECTIONAL STUDY

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ABSTRACT

Introduction

Several studies have reported sub-optimal efficacy of direct-acting antivirals (DAA) to treat hepatitis C virus (HCV) subtypes endemic to Sub-Saharan Africa (SSA) and Southeastern Asia (SEA). The extent of this issue in individuals with HIV/HCV from SSA or SEA residing in Europe is unknown.

Methods

We retrospectively analyzed data from several prospective European cohorts of people living with HIV. We included individuals with HIV/HCV who originated from SSA or SEA, were treated with interferon-free DAA, and had an available HCV RNA result ≥12 weeks after end of treatment. The primary outcome was sustained virological response at least twelve weeks after end of treatment (SVR-12).

Results

Of the 3293 individuals with HIV/HCV treated with DAA and with available SVR-12 data, 142 were from SSA (n=64) and SEA (n=78). SVR-12 was achieved by 60 (94%, 95% CI 86-98%) individuals from SSA and 76 (97%, 95% CI 92-99%) from SEA. The genotypes of the six individuals failing DAA treatment were 2, 3a, 3h, 4a, 4c, and 6j. For two of the four unsuccessfully treated individuals with available sequence data at treatment failure, NS5A resistance-associated substitutions were present (30R/93S in an individual with genotype 4c and 31M in an individual with genotype 6j).

Conclusions

SVR-12 rates were high in individuals with HIV/HCV residing in Europe and originating from regions where intrinsically NS5A-resistant HCV strains are endemic. HCV elimination for this population in Europe will unlikely be hampered by sub-optimal DAA efficacy.

INTRODUCTION

The majority of hepatitis C virus (HCV) infections worldwide are found in low- and middle-income countries (LMIC), namely for sub-Saharan Africa (SSA) and southeastern Asia (SEA).[1] Trials evaluating the efficacy of current direct-acting antivirals (DAA) have been predominately conducted in high-income countries. The HCV geno-/subtypes studied in these trials were common to those of the global epidemic (i.e. 1a/b, 2a/b, 3a, 4a/d), but not to those specific to SSA and SEA.[2] Clinical trials from LMIC and real-world studies from Western countries have recently shown sub-optimal DAA efficacy for several HCV subtypes, termed 'non-epidemic' (i.e. other than 1a/b, 2a/b, 3a, 4a/d).[2–6] These included a trial in Southeastern Asia where 76% (32/42) of individuals with genotype 3b achieved SVR-12, a trial in Rwanda where 56% (27/48) of individuals with genotype 4r achieved SVR-12, and a real-world study from London, United Kingdom where SVR-12 rate among African patients with non-epidemic genotype 1 subtypes was 75% (21/28).[3,5,7] The most recent European Association for the Study of the Liver (EASL) HCV guidelines has therefore recommended NS5B sequencing to determine genotype and subtype for migrants from countries where non-epidemic subtypes are prevalent.[8]

DAA efficacy for non-epidemic HCV subtypes has been rarely examined in individuals with HIV/HCV.[3–6] This is concerning given that the prevalence of HIV/HCV co-infection is high for several countries in SSA and SEA.[9–11] Furthermore, migrants from these regions comprise a substantial part of individuals living with HIV in Europe.[12,13] Sub-optimal DAA efficacy in individuals harboring HCV genotypes from these regions could then impede HCV elimination goals for the entire population with HIV/HCV in Europe. Real-world data on the prevalence of HCV geno-/subtypes and DAA treatment outcomes would help assess the population-level risk of treatment failure and in establishing whether NS5B sequencing should be broadened, particularly for HIV/HCV co-infection.

The objective of this study was therefore to investigate the real-world efficacy of DAA treatment in individuals with HIV/HCV originating from SSA and SEA in multiple European cohorts of people living with HIV.

METHODS

Study design and population

Data were obtained from several longitudinal, observational, prospective cohorts of persons living with HIV in Europe. These were from EuroSIDA (including data from clinics from Southern, Western, Northern, Central and Eastern Europe, last data extraction: July 2020),[14] ATHENA[15] (the Netherlands, last data extraction: May 2021), and SHCS[13] (Switzerland, last data extraction: June 2021). All participating cohorts included individuals with confirmed HIV-1 infection who were over the age of 18, without restrictions on HIV RNA or CD4+ cell count levels. HCV RNA testing was conducted according to routine clinical practice. To account for overlap between cohorts, data from any participant included in ATHENA or SHCS who also participated in EuroSIDA were only considered once.

From each cohort, we initially selected HCV RNA-positive individuals who were treated with an interferon-free DAA regimen. Subsequently, individuals originating from either SSA or SEA were selected, while those originating from an unspecified country or region in Africa or Asia were not considered further. Finally, individuals who had an available HCV RNA result at least twelve weeks after the end of interferon-free DAA treatment and before starting any new HCV regimen were included in the analysis. Both primary HCV infection and re-infections were considered in the analysis.

Data collection

Data were collected on the number of individuals with HIV/HCV treated with an interferon-free DAA regimen, the number of DAA-treated individuals with an available sustained virological response result twelve weeks after treatment (SVR-12) and of these, the number who achieved SVR-12. These data were collected for the complete cohort and for individuals originating from SSA and SEA.

Aggregated data of DAA-treated individuals who had an SVR-12 result and originated from SSA or SEA were retrieved and included: HCV genotypes and subtypes, age, sex, routes of HIV acquisition, presence of cirrhosis (based on the cohort-specific definition), region of origin, detectable or undetectable HIV RNA status, CD4+ cell count and DAA regimen used. Non-epidemic HCV geno-/subtypes were defined as those other than 1a/b, 2a/b, 3a, and 4a/d. Genotype results with missing or multiple subtypes were labeled as unassigned genotypes, except for those belonging to genotype 5 (no assigned subtypes known) or genotype 6 (no epidemic subtypes). HCV genotypes were determined via commercially available or in-house assays, yet data on the type of assay used for each participant were unavailable.

Finally, limited, anonymous, individual data were collected on included individuals who failed DAA treatment and included: region of origin, HCV treatment history, presence of advanced fibrosis or cirrhosis, presence of renal insufficiency (defined as an estimated glomerular filtration rate <30 ml/min/1.73m^2 according to formulas used in the cohort), HCV geno-/subtype, failed DAA regimen, resistance-associated substitutions (RAS) and re-treatment data. Advanced fibrosis or cirrhosis was defined as a Fibroscan® measurement ≥9.5 kPa for ATHENA and by a cohort-specific definition for EuroSIDA.[16] Liver fibrosis data were not available for SHCS.

Statistical analysis

Descriptive data are reported as either percentage or mean (±standard deviation). For SVR-12 rates, 95% confidence intervals (CI) were calculated using the Jeffreys method. Means and standard deviations were re-calculated from aggregated data to represent the study population including all cohorts. All characteristics are reported for the time at which the first interferon-free DAA treatment regimen was commenced, or until one year after for laboratory values. SVR-12 rates were calculated for the complete SSA and SEA groups and stratified for non-epidemic, epidemic and unassigned genotypes. In sensitivity analyses, SVR-12 rates were calculated by assuming that all unassigned genotypes were either non-epidemic or epidemic genotypes and by assuming that individuals from SSA harboring genotype 4 with an unknown subtype had non-epidemic genotypes, as these are unlikely to be genotype 4a/d infections if acquired in SSA.[17,18]

RESULTS

In total, 3856 individuals with HIV/HCV coinfection were treated at least once with an interferon-free DAA regimen, of whom 3293 (85%) had an available SVR-12 HCV RNA result (Figure 1). This included 64 and 78 individuals from SSA and SEA, respectively. Among the 142 individuals from SSA or SEA (Table 1), HIV was mainly acquired through heterosexual contact (*n*=52, 37%) or among men who have sex with men (*n*=51, 36%). Of the 122 individuals with known liver fibrosis status, 28 (23%) had evidence of advanced fibrosis or cirrhosis.

Non-epidemic genotypes were identified in 20% (*n*=13/64) individuals from SSA and 4% (*n*=3/78) from SEA (Table 2). For individuals originating from SSA, the most common genotypes were genotype 4 (*n*=26, 41%) and genotype 1 (*n*=23, 36%) with the most common subtype being 1a (*n*=18, 28%). Twenty-one (33%) individuals from SSA had a genotype with unassigned subtype, mainly those harboring genotype 4 (*n*=15, 23%) or genotype 2 (*n*=4, 6%). For individuals originating from SEA, the most common genotypes were genotype 1 (*n*=58, 74%) and genotype 3 (*n*=10, 13%) with the most common subtypes being 1a (*n*=42, 54%), 1b (*n*=10, 13%) and 3a (*n*=7, 9%). Ten (13%) individuals from SEA had a genotype with unassigned subtype.

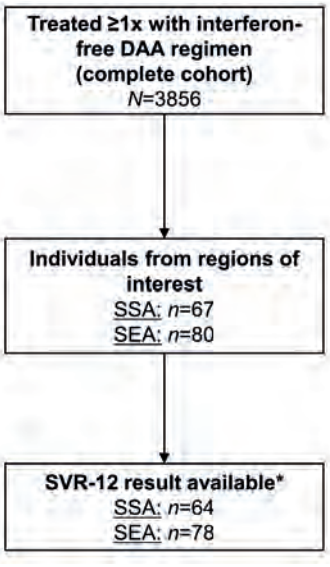

Figure 1. Flowchart
*Reason for SVR-12 HCV RNA results being unavailable: awaiting SVR-12 HCV RNA measurement (n=2), HCV RNA missing (n=2), discontinued cohort participation soon after HCV treatment (n=1).
Abbreviations: DAA: direct-acting antivirals. SSA: Sub-Saharan Africa. SEA: Southeastern Asia. SVR: sustained virological response.

Table 1. Demographic and clinical description of individuals with HIV/HCV from SSA or SEA treated with interferon-free DAA and with available SVR-12 data.

	(N=142)
Age, years (mean, SD)	47 (10)
Female sex	44 (31%)
Routes of HIV acquisition	
Men who have sex with men	51 (36%)
Injecting drug use	25 (18%)
Heterosexual contact	52 (37%)
Other	6 (4%)
Unknown	8 (6%)
Advanced fibrosis or cirrhosis	
No	94 (66%)
Yes	28 (20%)
Missing	20 (14%)
Region of Origin	
Eastern Africa	19 (13%)
Western Africa	11 (8%)
Southern Africa	7 (5%)
Middle Africa	27 (19%)
Eastern Asia	7 (5%)
South-eastern Asia	53 (37%)
Southern Asia	18 (13%
Undetectable HIV RNA (<50 copies/mL)	
No	6 (4%)
Yes	134 (94%)
Missing	2 (1%)
CD4+ cell count, /mm^3 (mean, SD)	633 (286)
DAA regimen	
Sofosbuvir/ledipasvir	64 (45%)
Sofosbuvir/daclatasvir	28 (20%)
Sofosbuvir/velpatasvir	13 (9%)
Elbasvir/grazoprevir	13 (9%)
Glecaprevir/pibrentasvir	10 (7%)
Sofosbuvir/simeprevir	9 (6%)
Sofosbuvir/ribavirin	3 (2%)
Dasabuvir/ombitasvir/paritaprevir/ritonavir	2 (1%)

All characteristics are reported for the time at which the first interferon-free DAA treatment regimen was commenced, or until one year after for laboratory values. Data were obtained from the EuroSIDA (including data from clinics from Southern, Western, Northern, Central and Eastern Europe)[14], ATHENA[15] (the Netherlands), and SHCS[13] (Switzerland).
Abbreviations: SD: standard deviation. DAA: direct-acting antivirals.

Table 2. Distribution of HCV genotypes of individuals with HIV-HCV from SSA or SEA treated with interferon-free DAA and with available SVR-12 data.

	Subtype	Sub-Saharan Africa (n=64)	Southeastern Asia (n=78)
Genotype 1		**23 (36%)**	**58 (74%)**
	a	18	42
	b	2	10
	c	1	0
	Unknown	2	6
Genotype 2		**8 (13%)**	**1 (1%)**
	a	2	0
	c	2	0
	Unknown	4	1
Genotype 3		**2 (3%)**	**10 (13%)**
	a	1	7
	h	1	0
	Unknown	0	3
Genotype 4		**26 (41%)**	**3 (4%)**
	a	2	1
	c	2	0
	d	1	2
	e	2	0
	f	2	0
	g	1	0
	v	1	0
	Unknown	15	0
Genotype 5		**1 (2%)**	**0**
Genotype 6		**0**	**3 (4%)**
	a	0	2
	j	0	1
Unknown		**4 (6%)**	**3 (4%)**

Data were obtained from the EuroSIDA (including data from clinics from Southern, Western, Northern, Central and Eastern Europe)[14], ATHENA[15] (the Netherlands), and SHCS[13] (Switzerland).

The most commonly prescribed DAA regimen was sofosbuvir/ledipasvir (*n*=63, 44%), while 23 (16%) individuals were treated with pan-genotypic regimens (i.e. either sofosbuvir/velpatasvir or glecaprevir/pibrentasvir). Among those with an available SVR-12 result, the SVR-12 rates were 94% (*n*=60/64, 95% CI 86-98%) for individuals originating from SSA and 97% (*n*=76/78, 95% CI 92-99%) for those from SEA. SVR-12 rates were 98% (*n*=86/88, 95% CI 93-100%) for individuals with epidemic genotypes, 81% (*n*=13/16, 95% CI 58-94%) for individuals with non-epidemic genotypes, and 97% (*n*=30/31, 95% CI 86-100%) for those with genotypes with unassigned subtype. When assuming that all unassigned genotypes were either epidemic or non-epidemic genotypes, SVR-12 rates were 97% (*n*=116/119, 95% CI 93-99%) and 91% (*n*=43/47, 95% CI 81-97%), respectively. When assuming that individuals from SSA harboring genotype 4 infection with an unknown subtype had an non-epidemic genotype, the SVR-12 rate for individuals from SSA with a non-epidemic genotype was 93% (*n*=26/28, 95% CI 79-98%).

Table 3. Individuals with HIV/HCV from Sub-Saharan Africa or Southeastern Asia failing interferon-free DAA treatment

	#1	#2	#3	#4	#5	#6
Region of origin	Middle Africa	South-Eastern Asia	East Africa	South East Asia	Middle Africa	East Africa
HCV treatment history	No	No	1	1	No	1
Cirrhosis	No	Unknown	No	Yes	No	Yes
eGFR<30	No	Unknown	No	No	No	No
Geno-/Subtype	4c	6j	3h	3a	2[†]	4a
Failed DAA regimen	SOF/LDV	ELB/GRZ	SOF/VEL	SOF/DAC	SOF/LDV	SOF/DAC
Treatment adherence[‡]	N/A	100%	Good	Good	Good	Good
Pre-DAA RAS	N/A	N/A	N/A	N/A	N/A	N/A
Post-DAA RAS	NS5A: 30R, 93S	NS3: 170V NS5A: 31M	NS3: 166S, 175M NS5A, NS5B: None[§]	NS3, NS5A, NS5B: None	N/A	N/A
Successful re-treatment	Yes	Yes	Yes	No	Yes	Not re-treated
DAA regimen used for re-treatment	GLE/PIB	SOF/VEL/VOX	SOF/VEL/VOX	SOF/GLE/PIB	SOF/DAC/rbv	

[†]Subtype was missing for this individual. [‡]As reported by the treating physician. [§]NS5B sequence was available from position 217 to 346. Presence of RAS was therefore not assessed for several NS5B positions where genotype 3 RAS can occur, e.g. 150, 159 and 206.
Abbreviations: HCV: hepatitis C virus. eGFR: estimated Glomerular Filtration Rate. DAA: direct-acting antiviral. SOF: Sofosbuvir. LDV: Ledipasvir. ELB: Elbasvir. GRZ: Grazoprevir. VEL: Velpatasvir. DAC: Daclatasvir. N/A: not available. RAS: resistance-associated substitution. GLE: Glecaprevir. PIB: Pibrentasvir. VOX: Voxilaprevir. Rbv: Ribavirin.

Of the six individuals with unsuccessful DAA treatment (Table 3), three had a non-epidemic HCV genotype (3h, 4c, 6j), two had genotypes commonly encountered in the global epidemic (3a, 4a) and one had a genotype with unassigned subtype (2). Four individuals were successfully re-treated, one has not yet received re-treatment and one individual with cirrhosis was unsuccessfully re-treated with sofosbuvir/glecaprevir/pibrentasvir. Post-treatment RAS data were available for four unsuccessfully treated individuals. Two of these individuals had clinically relevant NS5A RAS (i.e., 30R/93S and 31M).

DISCUSSION

Previous studies reporting decreased DAA efficacy for certain HCV subtypes endemic to SSA and SEA have included very few individuals with HIV/HCV.[3–6] In this large, European study of individuals with HIV/HCV treated with interferon-free DAAs and originating from regions where non-epidemic genotypes are prevalent, we observed high SVR-12 rates similar to those observed in other patient populations.[8] This result alone would suggest that reduced efficacy of DAAs is not common in this setting.

Eleven percent of individuals with HIV/HCV included in our study had a non-epidemic HCV genotype (SSA 20%, SEA 4%). This prevalence is almost certainly underestimated given that NS5B sequencing is not commonly performed in clinics across Europe and commercial HCV genotyping assays often result in missing or incorrect subtypes, especially for genotypes 2, 4 and 6.[19] An additional 22% (SSA 33%, SEA 13%) had an unassigned subtype, of whom a substantial proportion was likely harboring a non-epidemic genotype. In comparison, another study among individuals with mainly HCV mono-infection (9% HIV/HCV) from SSA living in London, the United Kingdom, demonstrated a much higher prevalence of non-epidemic genotypes as determined by a commercial assay (56%).[3] Additionally, our study sample did not include HCV subtypes that intrinsically harbor NS5A-resistant mutations (e.g. 1l, 3b, 3g, 4r, 6u, 6v).[6,8] These observations, alongside the high SVR-12 rate observed in our study, could indicate a lower frequency of intrinsically resistant HCV strains among individuals with HIV/HCV. This suggests that decreased DAA efficacy due to intrinsically resistant HCV strains, as observed in individuals from SSA or SEA with HCV mono-infection, might not be pervasive in individuals with HIV/HCV from SSA or SEA living in Europe.

It is difficult to determine whether included individuals acquired HCV in the country of origin or after moving to Europe, as we lacked sufficient virological data and data on risk behavior of participants while residing in Europe. Although data on HCV transmission in migrant populations are not available, a study modeling HIV transmission in migrants from Asia and Africa demonstrated that HIV is acquired in Europe for 32%-45% of cases.[20] We did observe several non-epidemic genotypes that are common to SSA or SEA in our study population, suggesting that some HCV transmission occurred prior to migration or within specific communities of similar origin in Europe. Nevertheless, a substantial part of our study population harbored genotypes and subtypes frequently circulating in Europe and not in SSA or SEA (e.g., genotype 1a was the most common subtype in DAA-treated individuals from SSA, while this genotype is uncommon in large parts of this region), thus many were likely to have acquired HCV in Europe.[1] This finding should be kept in mind when considering the high SVR rates observed in our study, and it should

be stressed that our results are by no means representative for individuals with HIV/HCV living in SSA or SEA.

Nevertheless, these results have important clinical and public health implications for the European setting. DAA failure was uncommon in our study and many individuals had an epidemic genotype that was likely acquired in Europe. The 81% SVR rate in individuals harboring non-epidemic genotypes might potentially suggest lower effectiveness of DAA therapy in this population; however, this rate only reflects a small number of individuals and would require more data to confirm its clinical relevance. Moreover, only 16% of our study population, which includes one patient failing DAA treatment, were given the pangenotypic DAA regimens that are currently standard of care in Europe and contain more potent NS5A inhibitors. The SVR-12 rates observed in current clinical practice might be even higher than those reported in our study. Our results imply that HCV elimination for this population in Europe will unlikely be hampered by sub-optimal efficacy of DAAs to strains harboring naturally occurring NS5A-resistant RAS.

Currently, the EASL recommends using NS5B sequencing as the standard method to determine baseline HCV genotypes in all individuals with HCV originating from SSA or SEA.[8] However, as we observed high SVR-12 rates in our study, it can be questioned whether this method is uniformly required for individuals with HIV/HCV from SSA or SEA. With an SVR-12 rate above 95%, approximately one in twenty of these individuals could potentially benefit from a tailored DAA treatment regimen if a non-epidemic genotype were detected. NS5B sequencing might be worthwhile in settings where it is already part of standard care, but not for those where sequencing methods are not readily available and additional costs or time are required. Deciding to use NS5B sequencing for individuals with HIV/HCV originating from SSA or SEA should be considered in light of the characteristics of the patient (e.g. transmission route and assumed location of acquiring HCV) and resources of the healthcare structure (e.g. availability of sequencing methods).

To our knowledge, this study provides the first real-world data on DAA efficacy for individuals with HIV/HCV living in Europe and originating from countries where HCV strains intrinsically resistant to NS5A inhibitors are endemic. Nevertheless, our study has several limitations. Due to a lack of available samples, we were unable to sequence all HCV strains of included participants to more accurately determine genotype/subtype and presence of resistance-associated substitutions. Genotyping assays based on the 5'UTR strand of HCV regularly lead to missing or incorrect classification of subtype or occasionally even genotype.[19] Additionally, SVR results were missing for five DAA-treated individuals. The SVR-12 rate would then be lower if considering these individuals as

failing DAA treatment (i.e., 93% of those treated with DAA achieved SVR-12). Furthermore, due to privacy regulations, we were unable to collect data on the specific countries of origin, thereby limiting the interpretability of our results. In addition, since only aggregated data were available, we were unable to assess differences in SVR-12 rate between individuals with different HIV transmission routes or specifically for individuals with cirrhosis. Finally, individuals included in this real-world cohort were treated with a very heterogeneous array of DAA regimens. To conclude definitively on DAA efficacy in individuals with HIV/HCV from SSA and SEA living in Europe, future research should focus on more accurately determining genotypes/subtypes and within which groups HCV transmission is occurring.

CONCLUSIONS

DAA efficacy in people with HIV/HCV originating from SSA or SEA and living in Europe is high. Although the limited number of participants with genotypes of concern and the lack of data on location of HCV acquisition limit conclusions on DAA efficacy for individuals with HIV/HCV residing in SSA or SEA, it seems unlikely that suboptimal response to DAAs specific to these individuals could become a complicating factor for overall HCV elimination in Europe in the near future.

Declaration of interest

C.I. has received research funding from Gilead, not related to this study. AM has received honoraria, travel support and/or consultancy fees from ViiV, Gilead and Eiland and Bonnin, all outside the submitted work. A.M. has received honoraria, travel support and/or consultancy fees from ViiV, Gilead and Eiland and Bonnin, all outside the submitted work. K.F. has received honoraria from GSK, Abbvie and Gilead, all outside the submitted work. G.W. has received unrestricted research grants form Gilead Sciences and Roche Diagnostics, unrelated to this work, as well as honoraria from ViiV, MSD, Gilead sciences (paid to his institution). M.C.'s institution received a conference grant from Gilead as well as research grants from Gilead, MSD and Viiv. M.S. has received grants for conference participation from Gilead and MSD. J.S.'s institution has received research support and consultancy fees from Gilead, and a speakers fee from Janssen Pharmaceuticals, independent from the submitted work. A.R. reports support to his institution for advisory boards and/or travel grants from MSD, Gilead Sciences, Pfizer and Abbvie, and a grant from Gilead Sciences. All remuneration went to his home institution and not to A.R. personally, and all remuneration was provided outside the submitted work. M.vdV. reports honoraria or research grants from Abbvie, Gilead, MSD, and ViiV Healthcare, all outside the submitted work. All other authors report no competing interests.

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PART III

CHALLENGES FOR HEPATITIS C VIRUS ELIMINATION IN THE NETHERLANDS

CHAPTER 8

HEPATITIS C ELIMINATION IN THE NETHERLANDS (CELINE): HOW NATIONWIDE RETRIEVAL OF LOST TO FOLLOW-UP HEPATITIS C PATIENTS CONTRIBUTES TO MICRO-ELIMINATION

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ABSTRACT

Background & Aims

The number of chronic hepatitis C virus (HCV)-infected patients who have been lost to follow-up (LTFU) is high and threatens HCV elimination. Micro-elimination focusing on the LTFU population is a promising strategy for low-endemic countries like the Netherlands (HCV prevalence 0.16%). We therefore initiated a nationwide retrieval project in the Netherlands targeting LTFU HCV patients.

Methods

LTFU HCV-infected patients were identified using laboratory and patient records. Subsequently, the Municipal Personal Records database was queried to identify individuals eligible for retrieval, defined as being alive and with a known address in the Netherlands. These individuals were invited for re-evaluation. The primary endpoint was the number of patients successfully re-linked to care.

Results

Retrieval was implemented in 45 sites in the Netherlands. Of 20,183 ever-diagnosed patients, 13,198 (65%) were known to be cured or still in care and 1,537 (8%) were LTFU and eligible for retrieval. Contact was established with 888/1,537 (58%) invited individuals; 369 (24%) had received prior successful treatment elsewhere, 131 (9%) refused re-evaluation and 251 (16%) were referred for re-evaluation. Finally, 219 (14%) were re-evaluated, of whom 172 (79%) approved additional data collection. HCV-RNA was positive in 143/172 (83%), of whom 38/143 (27%) had advanced fibrosis or cirrhosis and 123/143 (86%) commenced antiviral treatment.

Conclusion

Our nationwide micro-elimination strategy accurately mapped the ever-diagnosed HCV population in the Netherlands and indicates that 27% of LTFU HCV-infected patients re-linked to care have advanced fibrosis or cirrhosis. This emphasizes the potential value of systematic retrieval for HCV elimination.

INTRODUCTION

Achieving hepatitis C virus (HCV) elimination as a global health threat has been a priority of many countries since the World Health Organisation published their elimination targets.[1] In low-endemic countries, like the Netherlands (prevalence 0.16%),[2] micro-elimination may be a favourable approach.[3]

In the Netherlands, HCV is restricted to key populations such as people who inject(ed) drugs, migrants from HCV endemic countries, men who have sex with men and people with inherited bleeding disorders.[2] These key populations are commonly identified as targets for HCV micro-elimination initiatives. A population worthy of attention are people with HCV who have been lost to follow-up (LTFU). Despite earlier diagnosis they dropped out of the continuum of care before adequate management had been delivered or after antiviral treatment without formal proof of HCV eradication.

Several Dutch regional projects demonstrated that the LTFU rate in people with HCV runs up to 30%.[4-6] These pilot studies drove the development of the current micro-elimination project "Hepatitis C Elimination in the Netherlands (CELINE)", that aimed to retrieve and re-evaluate LTFU HCV patients in a nationwide manner. Successful implementation would support the concept of micro-elimination in the LTFU HCV population as a tool towards achieving the World Health Organisation (WHO) hepatitis C elimination targets in low endemic countries.[1]

METHODS

Study setting and ethics

Care for patients with viral hepatitis in the Netherlands is covered by mandatory health insurance and centred in certified hepatitis treatment centres. Between 2018 and 2020 all 46 certified centres in the Netherlands were invited to participate. If a treatment centre had executed an independent, regional retrieval project, the outcomes were included in this study once a data sharing agreement was reached. Other non-certified centres were invited to participate if there was a close collaboration with a certified hepatitis treatment centre.

Local approval was provided by all participating centres. Retrieval and re-evaluation activities in the CELINE project were part of standard care. Collected clinical data of successfully retrieved patients were analysed for research purposes after patients provided informed consent. Participation in the research was voluntary and did not influence clinical care.

Study population and retrieval strategy

The study protocol has been described in detail previously.[7] An overview can be seen in Supplementary Figure 1. In short, patients with a previously diagnosed HCV infection who had become LTFU were identified based on laboratory results and medical chart review. Patients with severe comorbidity or short life expectancy resulting in an expected lack of benefit from antiviral treatment were excluded. The Municipal Personal Records Database was queried to identify patients eligible for retrieval, defined as being alive and with a registered address in the Netherlands. Subsequently, patients eligible for retrieval were invited by letter for a re-evaluation visit at a hepatitis treatment centre of their choice. Patients younger than 18 were invited for re-evaluation but were not included in data collection.

Study endpoints and statistical analysis

The primary outcome was the number of LTFU patients successfully re-linked to care, defined as at least one visit at the outpatient clinic of a certified hepatitis treatment centre. Secondary outcomes included the total number of diagnosed and number of LTFU individuals, case ascertainment rate (i.e. established contact with invited patients), proportion of HCV-viraemic patients among re-evaluated patients, reasons for becoming LTFU, mode of HCV transmission, proportion of individuals with at least advanced liver fibrosis (liver stiffness measurement value ≥9.5 kPa or radiological, histological or clinical signs of cirrhosis [8, 9]) among HCV-viraemic patients, and DAA treatment outcome.

Descriptive data are reported as percentage, mean (+/- standard deviation; SD) or median (with interquartile range; IQR). Analyses were performed using IBM SPSS Statistics® version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

RESULTS

In total, CELINE was implemented in 45 sites, including 39/46 (85%) of certified hepatitis treatment centres in the Netherlands, five non-certified centres and one laboratory mainly serving primary care. Six centres with previously executed regional projects were included.[4-6] Among the remaining seven hepatitis treatment centres not included in the analyses, five centres had initiated own retrieval initiatives prior to CELINE roll-out and were not able to share data while two centres refused participation.

A total of 20,183 previously diagnosed patients were identified using laboratory records spanning median 14 years (IQR 11 – 17 years). The majority (n=10,929, 54%) had already been successfully treated or spontaneously cleared infection (Figure 1). In total 1,537 patients (8%) were identified as LTFU and eligible for retrieval.

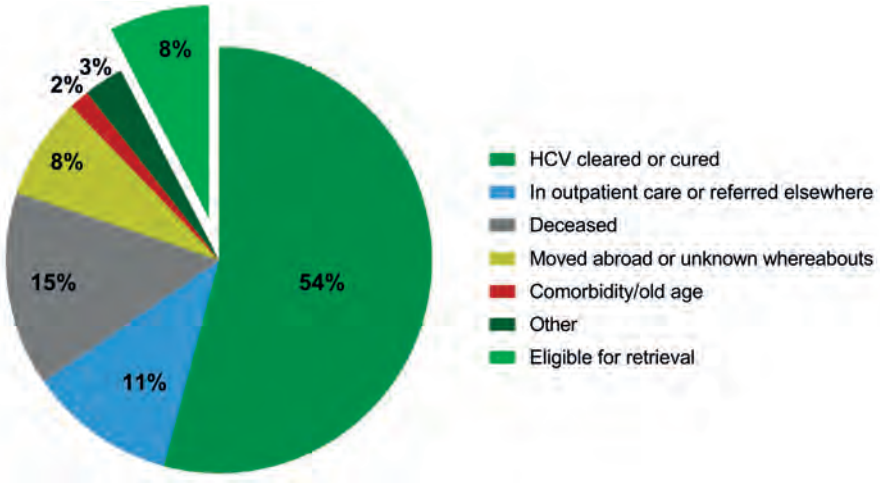

Figure 1. Outcome of 20,183 anti-HCV positive patients, identified in 45 centres
Abbreviations: HCV, hepatitis C virus.

Contact could not be established in 649 cases (Figure 2), resulting in a case ascertainment rate of 58% (888/1,537). Of the 1,537 invited patients, 369 (24%) were already cured or in care elsewhere and 131 (9%) refused to be re-linked to care. In total, 251 (16%) patients were referred, of whom 219 (87%) attended their visit. Three of the remaining 32 patients have their screening visit planned and 29 disregarded their scheduled visit.

Of the 219 screened individuals, 172 (79%) provided informed consent for data collection (Table 1). One hundred and ten patients ever had a liver stiffness measurement (n=51) and/or abdominal ultrasound (n=105), of whom 14 patients (13%) had evidence of

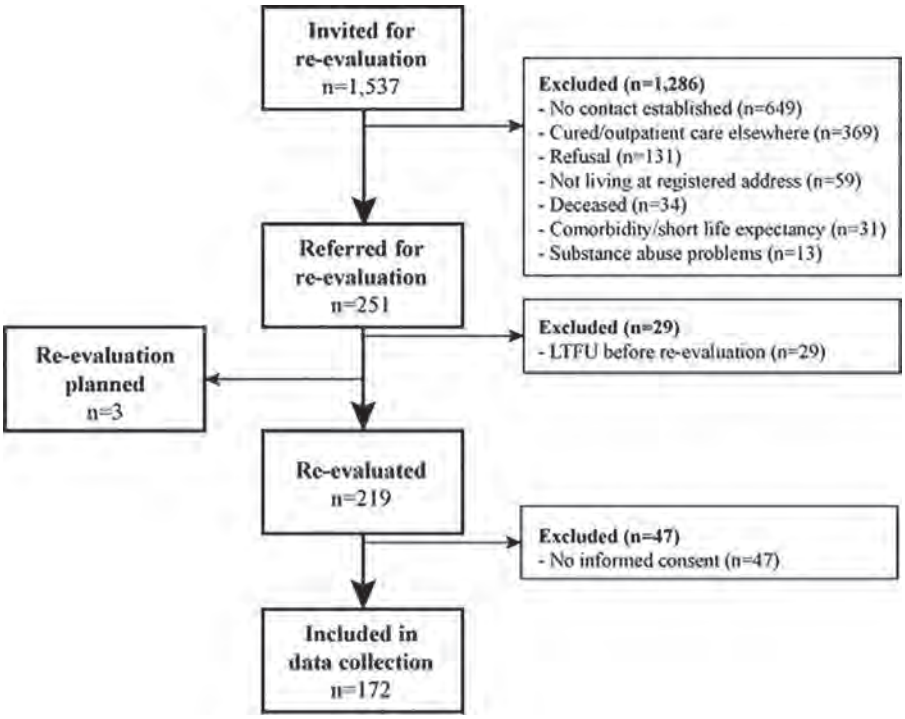

Figure 2. Flowchart of patients eligible for retrieval, who were invited for re-evaluation
Abbreviations: LTFU: lost to follow-up.

advanced liver fibrosis or cirrhosis. One LTFU patient had a prior focal hepatocellular carcinoma (HCC). Among the re-evaluated patients, 27 patients (16%) never had a prior HCV-related appointment at an outpatient clinic and 18 patients (11%) reported being unaware of their possible HCV infection. HCV-RNA was positive in 12 of these 18 patients (67%), of whom three (25%) had advanced fibrosis or cirrhosis at the re-evaluation visit.

In total, 143/172 patients (83%) tested HCV-RNA positive at re-evaluation (Table 2). HCV-RNA was negative in 24 patients (14%) and not (yet) tested in five (3%). Among the 167 patients with a known HCV-RNA status at re-evaluation, HCV-RNA was positive in 127/145 (88%) of those with a positive HCV-RNA status before becoming LTFU and 16/27 (59%) of those with positive HCV antibodies with unknown HCV-RNA status. At re-evaluation, none of the patients tested HIV-positive, but two patients (1%) had a newly diagnosed hepatitis B virus infection. Among HCV-RNA positive patients, 38 (27%) had advanced fibrosis or cirrhosis, of whom two were classified as Child-Pugh B and one as Child Pugh C. Additionally, two patients were diagnosed with an HCC at the time of the re-evaluation visit and another three patients developed an HCC during the period after their re-evaluation visit.

Table 1. Characteristics of re-linked patients who provided consent for data collection

	Re-linked patients (n=172)
Male sex	121 (70%)
Age in years at re-linkage to care (median, IQR)	58 (52 - 63)
Reason for becoming LTFU[1]	
Patient-related	76 (44%)
Therapy-related	44 (26%)
Care-related	41 (24%)
Other/unknown	11 (6%)
Years since last HCV-related hospital visit (median, IQR)	7 (4 - 11)
First-generation migrant	59 (34%)
Route of HCV transmission	
Injecting drug use	119 (69%)
Transfusion	18 (11%)
Other[2]	19 (1%)
Unknown	16 (9%)
(History of) substance abuse	
Injecting drug use	125 (73%)
Alcohol[3]	57 (33%)
Currently on opioid substitution therapy	50 (29%)
HCV treatment experience	44 (26%)[4]
(PEG-)Interferon	40 (23%)
Direct-acting antivirals	7 (4%)
HCV-RNA positive	143 (83%)

[1]Patient-related reasons for LTFU included: multiple no shows, therapy refusal, addiction, or imprisoned. Therapy-related reasons for LTFU included: no indication for therapy, lack of therapy options. Care-related reasons for LTFU included: no consequence given to HCV test, absent SVR check, HCV follow-up postponed due to other comorbidities or pregnancy, absent FU appointment, treatment deferred, waiting for a new appointment. [2]Nosocomial (5), needle prick injury (4), sexual (3), vertical (2), tattoo (1), injecting drug use or transfusion (1), injecting drug use or sexual (2), nosocomial or sexual (1). [3]Defined as >14 units/week for females and >21 units/week for males. [4]Several patients received both (PEG-)interferon and direct-acting antivirals.
Abbreviations: IQR: interquartile range; LTFU, lost to follow-up; HCV, hepatitis C virus; PEG: pegylated.

In 86% of HCV-RNA positive patients (123/143) DAA therapy was initiated. Sustained virological response (SVR) was achieved in all of the 91 individuals with a known HCV-RNA result twelve weeks after cessation of treatment. Four patients discontinued DAA, 10 finished the treatment course but became LTFU again without formal proof of SVR, and 27 patients are awaiting their SVR-12 result. Among the 20 patients who did not initiate

Table 2. Characteristics of HCV-RNA positive patients

	HCV-RNA positive (n=143)
Advanced fibrosis or cirrhosis at re-evaluation[1]	38 (27%)
HCV Genotype	
1a	61 (43%)
1b	29 (20%)
1, other/unknown subtype	4 (3%)
2	9 (6%)
3	27 (19%)
4	10 (7%)
unknown	3 (2%)
Co-infection	
Prior HBV (HBsAg-, anti-HBc+)	50 (35%)
Chronic HBV (HBsAg+)	2 (1%)
HIV	0 (0%)
DAA treatment initiated after retrieval	123 (86%)
SOF/LDV	10 (8%)
SOF/VEL	28 (23%)
GLE/PIB	67 (54%)
ELB/GRZ	13 (11%)
SOF/VEL/VOX	1 (1%)
Unknown	4 (3%)
Treatment outcome	
SVR	91 (75%)
Awaiting SVR-12 measurement	27 (22%)
Discontinued DAA therapy	4 (3%)

[1]Defined as a liver stiffness value ≥9.5 kPa or radiological, histological or clinical signs of cirrhosis.
Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; anti-HBc, antibodies against hepatitis B core antigen; HIV, human immunodeficiency virus; DAA, direct-acting antiviral; SOF, sofosbuvir; LDV, ledipasvir; VEL, velpatasvir; GLE, glecaprevir; PIB, pibrentasvir; ELB, elbasvir; GRZ, grazoprevir; VOX, voxilaprevir; SVR, sustained virological response.

DAA, six refused treatment, four became LTFU again, five had severe comorbidity or short life expectancy, two died, two had addiction problems, while one will start DAA treatment shortly.

DISCUSSION

CELINE was a nationwide retrieval project aiming to re-engage LTFU HCV patients with care. It was designed as a micro-elimination initiative to advance progress towards the WHO HCV elimination targets in the Netherlands. We demonstrated that the majority of individuals diagnosed in the past with HCV in the Netherlands had been cured prior to rollout of CELINE. We found that 8% was LTFU and eligible for retrieval. Advanced fibrosis or cirrhosis was diagnosed in 27% of HCV-RNA-positive retrieved individuals.

Our retrieval efforts resulted in 219 patients that we could re-link to care, corresponding to 14% of individuals invited for re-evaluation. Thus, the retrieval rate of our nationwide approach was within the bandwidth observed in several previously conducted regional Dutch projects.[4-6] Our study included the vast majority of hepatitis treatment centres in the Netherlands, thereby maximising its impact and providing valuable insight into the epidemiology of patients ever diagnosed with HCV infection in the Netherlands. A higher number of re-linked patients might have been achieved if a national registry had been in place as this would improve adequate coordination of retrieval. Nevertheless, our retrieval was successful as a significant number of patients with advanced fibrosis or cirrhosis were re-linked to care. Furthermore, our study provided valuable insight into the HCV epidemiology of the Netherlands and demonstrated the feasibility of retrieval as a micro-elimination strategy. The robust and extensive framework that was laid out can serve as a blueprint for retrieval of patients with other diseases and in other countries.

The most common reasons for LTFU in our study were frequent no shows and refusal of HCV therapy. The most common reasons for unsuccessful retrieval were the inability to make contact with the patient, refusal of re-evaluation or substance abuse problems which complicated re-linkage to care. For these individuals it could be beneficial to perform retrieval as a standard annual or bi-annual procedure, instead of a one-time effort. Since current HCV treatment is highly effective, it could be argued that loss to follow-up is an unacceptable outcome and should be prevented or dealt with by all HCV care providers.

An important limitation of retrieval is that retrieval efforts are labour intensive. The current nationwide project was led by three full-time PhD candidates and required a commitment that is most likely impossible to meet by physicians and/or nurse consultants on top of the regular healthcare they provide. There are, however, some measures that can reduce the investments needed for future retrieval projects. First, make retrieval part of routine care and eliminate the collection of data for research purposes. This will bypass the laborious institutional review board process and will

thereby reduce workload. Second, implementing digital innovations such as a case-finding algorithm that successfully identifies diagnosed but untreated HCV patients further reduces workload.[10] Last but not least, the framework now laid out by CELINE will increase efficacy and reduce costs of future retrieval efforts.

CELINE results must be placed in the greater context of HCV elimination. A recent modelling study predicting the Netherlands' progress towards the WHO HCV elimination targets concluded that the Netherlands is currently on track to meet these targets by 2030.[11] However, this was only met under the assumption that annual HCV diagnosis and treatment rates were maintained at the 2019 levels. HCV micro-elimination in LTFU patients will mainly contribute to maintaining high treatment rates, especially if done repeatedly. In the Netherlands however, this contribution will be minor. Micro-elimination in other subpopulations in the Netherlands has already been highly successful, such as people living with HIV and people with inherited bleeding disorders [12, 13]. Increased efforts to find and cure HCV-viraemic individuals in other subpopulations, like migrants from high-endemic countries, PWID and incarcerated individuals, are needed.

To conclude, the majority of patients in the Netherlands who received the diagnosis of chronic HCV infection since the early 2000s has been cured. Our nationwide micro-elimination effort retrieved another 14% of the population who were LTFU and eligible for retrieval. LTFU patients have a high risk of advanced liver disease, illustrated by the 27% of HCV-RNA-positive retrieved individuals with evidence of advanced liver fibrosis or cirrhosis. With CELINE we demonstrated that systematic retrieval provides great value for a better understanding of the HCV epidemiology. Additionally, we established a robust diagnostic pipeline targeting the LTFU population that is worthy of replication in other health care environments. As such, our study supports the view that micro-elimination through retrieval is feasible and contributes to HCV elimination.

DECLARATION OF INTEREST

C.J.I. has received research funding from Gilead, outside the submitted work. M.v.D. declares that the Radboudumc, on behalf of M.v.D., received honoraria due to participation in advisory boards of Abbvie and Gilead. R.d.K. declares that the Erasmus University Medical Centre, on behalf of R.d.K., received honoraria for consulting/speaking from Gilead, Janssen, Bristol-Myers Squibb (BMS), Abbvie, Merck Sharp & Dohme (MSD) and Roche and received research grants from Abbvie, Gilead, GlaxoSmithKline and Janssen. J.E.A. reports fees paid to the institution from Gilead, Janssen-Cilag, Abbvie, BMS, and MSD for advisory membership, all outside the submitted work. M.v.d.V. declares that Amsterdam UMC on behalf of M.v.d.V. received honoraria or research grants from Abbvie, Gilead, MSD, and ViiV Healthcare, all outside the submitted work. J.P.H.D. declares that the Radboudumc, on behalf of J.P.H.D., received honoraria or research grants from Novartis, Ipsen, Otsuka, Abbvie, and Gilead. J.P.H.D. served as consultant for Gilead and Abbvie, and in the last two years has been member of advisory boards of Otsuka, Norgine Gilead, BMS, Janssen, and Abbvie. All other authors report no conflict of interest.

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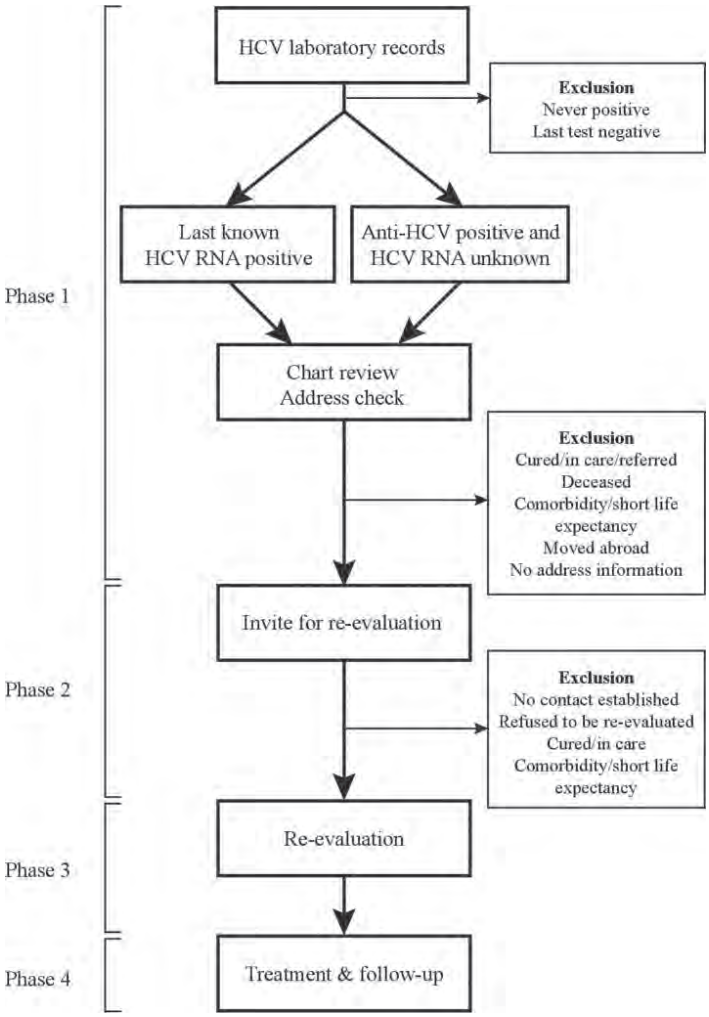
SUPPLEMENTARY MATERIAL



Supplementary figure 1. CELINE retrieval strategy
Abbreviations: HCV, hepatitis C virus.

CHAPTER 9

DIRECT-ACTING ANTIVIRAL TREATMENT FOR HEPATITIS C GENOTYPES UNCOMMON IN HIGH-INCOME COUNTRIES: A DUTCH NATIONWIDE COHORT STUDY

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On behalf of the HepNed Study Group

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ABSTRACT

Background

The majority of HCV infections are found in low- and middle-income countries, harboring many region-specific HCV subtypes. Nevertheless, direct-acting antivirals (DAA) trials were almost exclusively conducted in high-income countries, where mainly epidemically spread HCV subtypes are present. Recently, several studies demonstrated sub-optimal DAA efficacy for certain non-epidemic subtypes, which could hamper global HCV elimination. Therefore, we aimed to evaluate DAA efficacy in patients treated for a non-epidemic HCV genotype infection in the Netherlands.

Methods

We performed a nationwide retrospective study including patients treated with interferon-free DAA for a HCV genotype other than 1a/1b/2a/2b/3a/4a/4d. Genotype was determined by NS5B-region phylogenetic analysis. Primary endpoint was SVR-12. If stored samples were available, NS5A and NS5B sequences were obtained for resistance-associated substitutions (RAS) evaluation.

Results

We included 160 patients, mainly infected with non-epidemic genotype 2 (41%) and 4 (31%) subtypes. Most patients originated in Africa (45%) or South America (24%); 51 (32%) were cirrhotic. SVR-12 was achieved in 92% (140/152) of patients with available SVR-12 data. Only 73% (8/11) genotype 3 infected patients achieved SVR-12, the majority being genotype 3b patients with 63% (5/8) SVR. Regardless of SVR, all genotype 3b patients had 30K and 31M RAS.

Conclusions

DAA efficacy in most non-epidemic genotypes in the Netherlands seems reassuring. However, the low SVR-12 rate in subtype 3b infections is alarming, especially as it is common in several HCV endemic countries. Alongside earlier results, our results indicate that a remaining challenge for global HCV elimination is confirming and monitoring DAA efficacy in non-epidemic genotypes.

INTRODUCTION

Hepatitis C virus (HCV) infection is a global health problem, with an estimated worldwide prevalence of 71 million.[1] The virus is classified into eight major genotypes, further subdivided into over 67 subtypes.[2] The highest genetic diversity is observed in sub-Saharan Africa and Asia, due to low transmission rates and centuries-long persistence within the human population.[3] In high-income countries, the majority of HCV infections are caused by a limited number of HCV subtypes that in recent centuries rapidly spread via effective modes of transmission such as contaminated blood products, intravenous drug use, and unhygienic invasive medical procedures. In the Netherlands, these so-called epidemic subtypes, exemplified by subtypes 1a/1b/2a/2b/3a/4a/4d, account for approximately 90% of the HCV infections, although precise data are lacking.[4]

As most direct-acting antiviral (DAA) trials were executed in high-income countries, only rarely patients with non-epidemic HCV genotypes were included.[5] This lack of non-epidemic genotypes is also seen in online HCV sequence databases, in which genomic data from low- and middle-income countries (LMIC) are virtually absent.[6] Countries where these non-epidemic genotypes are endemic are among the countries with the highest HCV prevalence in the world.[1] Therefore, confirming the effectiveness of currently available DAA in these genotypes is of utmost importance for worldwide HCV elimination.

Two of the first DAA trials ever executed in LMIC give reason to dispute the assumption that DAA are as effective against non-epidemic HCV genotypes as they are against epidemic genotypes.[7,8] A study from Rwanda, including mainly endemic genotype 4 infections, showed a relatively low sustained virological response (SVR) rate of 87% with sofosbuvir (SOF)/ ledipasvir (LDV). This was mainly driven by a remarkably low SVR rate of 56% in 48 genotype 4r patients.[7] In a study from Asia, patients were treated with SOF/velpatasvir (VEL) resulting in a 95% SVR rate for the epidemic genotype 3a versus only 76% for the non-epidemic genotype 3b, despite similar baseline characteristics.[8]

Additionally, real-life data suggest a decreased DAA efficacy in certain non-epidemic HCV genotypes, as shown for genotype 6 in an Asian cohort of 85 patients treated with SOF/LDV with an SVR rate of 74% and for African patients with non-epidemic genotype 1 strains treated in London with a low SVR rate of 75%.[9,10] Furthermore, in an analysis from France of 537 patients who failed DAA treatment almost 10% harbored a rare non-epidemic genotype 1 strain and 5% genotype 4r, despite a low prevalence of these subtypes in the French population.[11] An explanation for the possible decreased efficacy

of DAAs could be that wild-type non-epidemic strains frequently contain amino acids associated with intrinsic resistance to DAAs, in particular in the NS5A-region.[12–15]

The recently updated EASL HCV treatment guideline acknowledges the lack of DAA treatment data for patients infected with subtypes inherently resistant to NS5A inhibitors, and mentions an urgent need for further data.[16] A sub-optimal DAA efficacy in certain HCV subtypes will hamper global elimination of HCV. So far, no real-world data has been published including a nationwide cohort consisting solely of patients with non-epidemic HCV genotypes. Therefore, the aim of this study was to investigate real-world efficacy of DAA treatment in patients with HCV genotypes other than 1a, 1b, 2a, 2b, 3a, 4a, and 4d in the Netherlands, in relation to baseline NS5A resistance-associated substitutions (RAS).

PATIENTS AND METHODS

Study design and population

This nationwide cohort study included patients infected with a non-epidemic HCV genotype treated with an interferon-free DAA regimen. Non-epidemic HCV genotypes were defined as genotypes and subtypes other than 1a/1b/2a/2b/3a/4a/4d. All laboratories performing HCV genotyping in the Netherlands were approached. All but one participated in the study: the Amsterdam University Medical Centers; Sanquin Diagnostics, Amsterdam; UMC Groningen, Groningen; LUMC, Leiden; Erasmus Medical Center, Rotterdam, and Maastricht UMC, Maastricht.

HCV genotyping

HCV genotype was determined by sequencing and phylogenetic analysis of the NS5B region, using a method and primers described before by Murphy *et al.*[17] Patients who were diagnosed with a non-epidemic subtype using a commercial assay (e.g. LIPA) or based on sequencing of the highly conservative 5'UTR region were only included if the presence of a non-epidemic subtype was confirmed by NS5B sequencing of a previously stored sample. Genotype sequences were submitted to GenBank (MW205243 - MW205375).

Software packages CodonCode Aligner (v8.0.2; CodonCode Corp., USA) and ClustalX v2.1[18] were used to edit and subsequently align obtained sequences against a reference set retrieved from the Los Alamos HCV sequence database.[19] Based on these alignments, genotype, and subtype were determined by constructing a maximum-likelihood phylogenetic tree created in MEGA v6.[20] If no subtype could be assigned using phylogenetic analysis, we used the HCV Blast tool[19] to find related sequences. A >90% match with a well-typed database sequence was considered sufficient to assign a subtype. If not, the subtype was labelled as unassigned and the closest related BLAST sequence was reported.

Data collection

Eligible patients were selected using a database search in the laboratory information system by the local medical (molecular) microbiologist. Subsequently, the treating physician was approached to provide clinical data. Finally, both virological and clinical data were supplied anonymized to the research coordinator. Demographic variables (age, gender, country of origin), clinical variables (co-morbidities, pre-treatment grade of liver fibrosis as assessed by Fibroscan®, HCV treatment history, and treatment outcome), and virological variables (genotype, baseline, and post-treatment RAS data if available)

were collected. Patients were labelled as being cirrhotic if reported as such by their treating physician or in case a liver stiffness measurement above 12.5 kPa was reported.

Patient Consent Statement

All data were supplied anonymized to the research coordinator by the respective treating physician. According to European privacy legislations and the Dutch Code of Conduct for the Use of Data in Health Research, the need for informed consent was therefore waived. The study was approved by the Medical Ethics Committee of the Amsterdam Medical Center, The Netherlands.

RAS analysis

For RAS analysis, a fragment of the NS5A and NS5B region was sequenced if stored plasma or serum was available. The sequenced fragment length was dependent on the specific primer set used, however minimally stretched from amino acid 23 to 129 for NS5A and 150 to 321 for NS5B sequences. It is debatable whether resistance-associated amino acid sequences that are wild-type for a specific subtype can be labelled as RAS, as they are not necessarily substitutions. However, both in literature and clinical practice these are often labelled as such. Therefore, we chose to define RAS as an amino acid substitution relative to the H77 genotype 1a reference sequence at a position associated with resistance, regardless of whether this amino acid is wild-type for the specific subtype. Positions associated with resistance were extracted from the Geno2pheno HCV database and the EASL guideline.[21,22] RAS sequences were submitted to GenBank (MW205376 - MW205507).

Outcome

Primary outcome was the SVR-12 rate for the first interferon-free DAA treatment, in all patients for whom the SVR-12 result was available. SVR-12 was defined as an undetectable level of HCV RNA 12 weeks after completion of DAA treatment. For sub-analyses, we calculated SVR-12 rate per genotype, cirrhotic versus non-cirrhotic, per region of origin (according to the standard area codes of the United Nations statistics division), for DAA regimens with and without NS5A inhibitor, and for pangenotypic second-generation DAA (SOF/VEL and glecaprevir (GLE)/pibrentasvir (PIB) versus older NS5A inhibitor-containing DAA regimens.

Statistical analysis

Data were analyzed using IBM SPSS statistics® v25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Descriptive data are reported as either percentages, mean (± standard deviation) or median (with interquartile range).

RESULTS

Non-epidemic genotypes

We included 160 patients treated with an interferon-free DAA regime for a non-epidemic HCV genotype. Three patients were treated in trial setting in 2012 or 2013, whereas the remaining 157 patients were treated between 2015 and 2019. Phylogenetic analysis revealed 28 different HCV subtypes in 121 patients, predominantly of subtypes 2 and 4 (Figure 1). In the remaining 39 patients, neither phylogenetic analysis nor BLAST search were able to assign a recognized HCV subtype. Twenty-five out of these 39 belonged to one of five previously described but officially unassigned genotype 2 clades originating from Suriname.[23] For the remaining 14 unassigned subtypes, BLAST results showing the closest related NS5B sequence with an assigned subtype are shown in supplementary file 2.

Baseline

Fifty-one (32%) of the included patients had liver cirrhosis, the vast majority Child-Pugh A (84%, Table 1). Most patients originated in Northern Africa (25%), South America (24%), or Sub-Saharan Africa (20%). At country level, most common origins were Suriname (23%), Egypt (18%), the Netherlands (10%), Democratic Republic Congo (7%), and Morocco (6%). Fifty individuals (31%) were treated with a pangenotypic second-generation DAA regime, 78 (49%) patients received a non-pangenotypic regime containing a NS5A inhibitor and 32 (20%) patients were treated without NS5A inhibitor. The latter were either genotype 2 infections treated with SOF + ribavirin (n=14, 9%) or patients treated with SOF/simeprevir (SIM, n=18, 11%).

Treatment results

SVR-12 data were available for 152 (95%) patients, of whom 140 (92%) achieved SVR-12. The eight patients without available SVR-12 result were either awaiting SVR-12 measurement at the time of data collection (n=5), lost to follow-up (n=2), or died before SVR-12 measurement (n=1). Treatment results per genotype and subtype are shown in Table 2 (further stratification per DAA regime is available in supplementary file 3). Non-epidemic genotype 3 infections showed the lowest SVR-12 rate, with 73% (8/11) being cured at the first treatment attempt. All three failures were genotype 3b infections, of whom one was cirrhotic. SVR-12 rate in genotype 3b patients was 63% (5/8). Notably, for three of the eight successfully treated genotype 3 infections, the intended treatment regime was optimized after baseline RAS analysis. One genotype 3b infected patient was treated successfully with GLE/PIB/SOF as first-line treatment, another genotype 3b infected patient was treated with GLE/PIB + ribavirin instead of intended SOF/VEL, and a genotype 3k infected, non-cirrhotic patient had ribavirin added to 12 weeks SOF/DAC. The SVR rate of genotype 3b patients with ribavirin added to their DAA regimen was 75% (3/4, all cirrhotic), compared to 50% without ribavirin (2/4, 1 cirrhotic), Besides

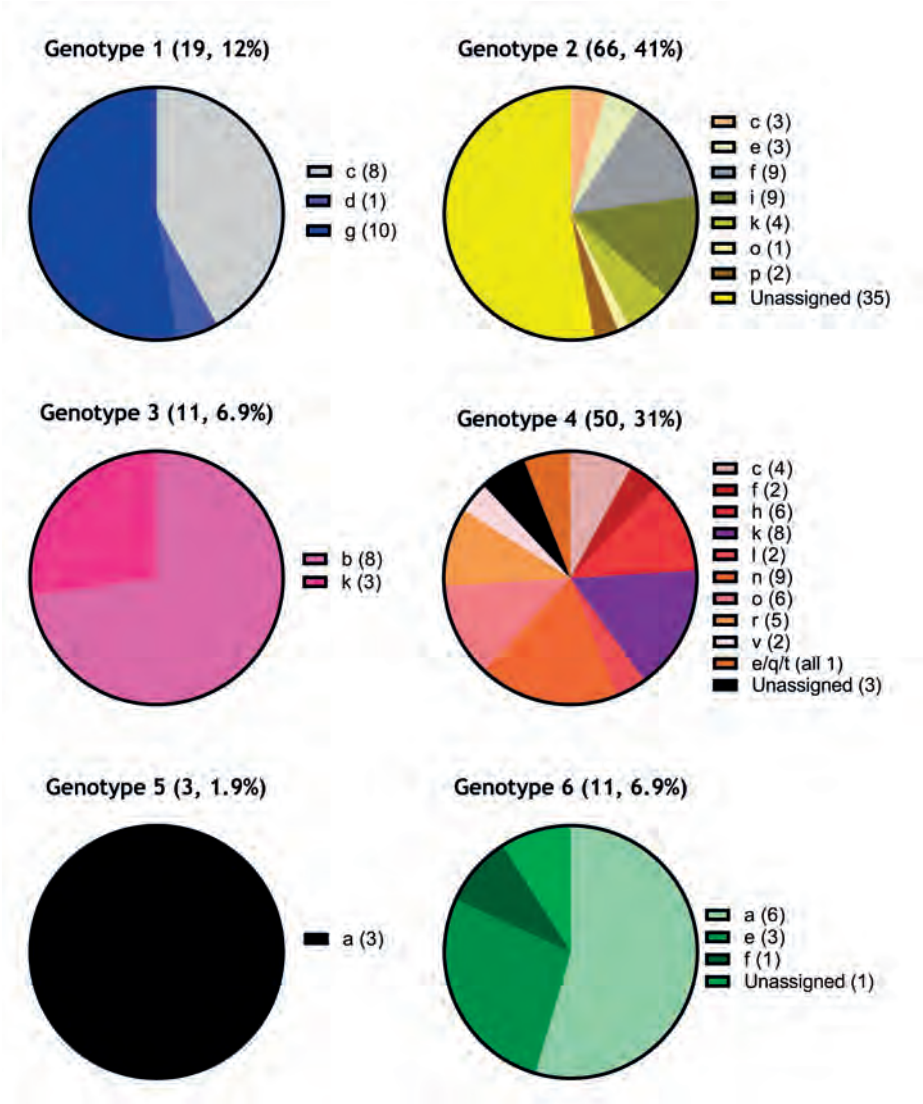

Fig. 1. Overview of the included genotypes and subtypes

genotype 3b, genotype 4n infections also showed a low SVR rate of 75% (6/8) due to two cirrhotic patients failing DAA treatment.

SVR-12 was 93% (112/120) for first treatment with and 88% (28/32) without a NS5A inhibitor-containing regime. For patients treated with a pangenotypic second-generation DAA regimen SVR-12 rate was 98% (44/45), compared to 91% (68/75) for patients treated with another NS5A inhibitor-containing regimen.SVR-12 was 89% (42/47) in cirrhotic and 93% (98/105) in non-cirrhotic patients. SVR-12 in cirrhotic patients treated with

Table 1. Patient and treatment characteristics

Patient characteristics	n = 160	Treatment characteristics	n = 160
Female gender	62 (39%)	**(PEG)-IFN treatment experience**[a]	32 (20%)
Age (median, IQR)	56 (49-64)	**DAA regimen**	
Hiv co-infection	5 (3%)	Sofosbuvir/ledipasvir	37 (23%)
Cirrhosis	51 (32%)	Sofosbuvir/velpatasvir	31 (19%)
Child-Pugh A/B/C	43 / 7 / 1	Sofosbuvir/daclatasvir	30 (19%)
Region of origin		Glecaprevir/pibrentasvir	18 (11%)
Northern Africa	40 (25%)	Sofosbuvir/simeprevir	18 (11%)
South America	39 (24%)	Sofosbuvir + ribavirin	14 (9%)
Middle Africa	16 (10%)	Elbasvir/grazoprevir	6 (4%)
Western Europe	16 (10%)	Ombitasvir/paritaprevir/ritonavir	4 (3%)
Eastern Africa	11 (7%)	Ombitasvir/paritaprevir/ritonavir/dasabuvir	1 (1%)
South-eastern Asia	11 (7%)	Sofosbuvir/glecaprevir/pibrentasvir	1 (1%)
Eastern Asia	6 (4%)	**NS5A inhibitor-containing regimen**	128 (80%)
Southern Asia	6 (4%)	**Ribavirin added to DAA regimen**	28 (18%)
Western Africa	5 (3%)		
Western Asia	4 (3%)		
Southern Europe	3 (2%)		
Unknown	3 (2%)		

Data are number (percentage) unless otherwise noted. PEG-IFN: PEGylated-interferon. DAA: direct-acting antiviral. NS5A: nonstructural protein 5a. [a]Three patients were treated unsuccessfully with PEG-IFN + DAA.

SOF/VEL or GLE/PIB was 100% (16/16). SVR-12 after treatment with SOF +ribavirin for non-epidemic genotype 2 infections was 79% (11/14) of cases, versus 98% (47/48) after NS5A-inhibtor containing DAA for genotype 2. Patient characteristics of the 12 patients that failed treatment are shown in Table 3.

Figure 2 shows the SVR-12 percentage per region of origin. The lowest SVR-12 rate was seen in patients originating in Southern Asia, with a 50% SVR-12 rate (3/6) due to two genotype 3b failures from Pakistan and one genotype 6f patient from India failing DAA treatment. In patients originating from Sub-Saharan Africa SVR-12 rate was 90% (27/30), however 93% (28/30) were cured with the first DAA regimen as one patient with detectable viral load at SVR-12 achieved SVR-24. All five patients with subtype 4r achieved SVR-12. Patients infected with one of the unassigned genotype 2 clades from Suriname had an SVR-12 rate of 96% (24/25).

Table 2. Treatment results stratified for included subtypes (n=160)

Genotype (n,%)	Subtype (n)	SVR-12 result (n/n)[a]
1 (19, 12%)		**100% (18/18)**
	c(8)	100% (7/7)
	d(1)	100% (1/1)
	g(10)	100% (10/10)
2 (66, 41%)		**93% (57/61)**
	c(3)	100% (3/3)
	e(3)	100% (3/3)
	f(9)	83% (5/6)
	i(9)	89% (8/9)
	k(4)	100% (4/4)
	o(1)	100% (1/1)
	p(2)	100% (2/2)
	clade I (12)[b]	92% (11/12)
	clade II (5)	100% (5/5)
	clade III (5)	100% (5/5)
	clade IV (1)	100% (1/1)
	clade V (2)	100% (2/2)
	unassigned (10)	88% (7/8)
3 (11, 7%)		**73% (8/11)**
	b(8)	63% (5/8)
	k(3)	100% (3/3)
4 (50, 31%)		**92% (44/48)**
	c(4)	100% (4/4)
	e(1)	100% (1/1)
	f(2)	100% (2/2)
	h(6)	100% (6/6)
	k(8)	88% (7/8)
	l(2)	100% (2/2)
	n(9)	75% (6/8)
	o(6)	100% (6/6)
	q(1)	100% (1/1)
	r(5)	100% (5/5)
	t(1)	100% (1/1)
	v(2)	0% (0/1)[c]
	unassigned(3)	100% (3/3)
5 (3, 2%)		**100% (3/3)**
	a(3)	100% (3/3)

Table 2. Treatment results stratified for included subtypes (n=160) (continued)

Genotype (n,%)	Subtype (n)	SVR-12 result (n/n)[a]
6 (11, 7%)		**91% (10/11)**
	a(6)	100% (6/6)
	e(3)	100% (3/3)
	f(1)	0% (0/1)
	unassigned(1)	100% (1/1)
Total (160)		**92% (140/152)**

SVR: sustained virological response. [a]Number of patients with SVR-12 result can be lower than number of included patients, as not all SVR-12 results were known at the moment of data collection. [b]These unassigned genotype 2 infections belong to previously described clades from Suriname[23]. [c]This patient had a detectable viral load of 38 IU/ml at SVR-12, and an undetectable viral load at SVR-24

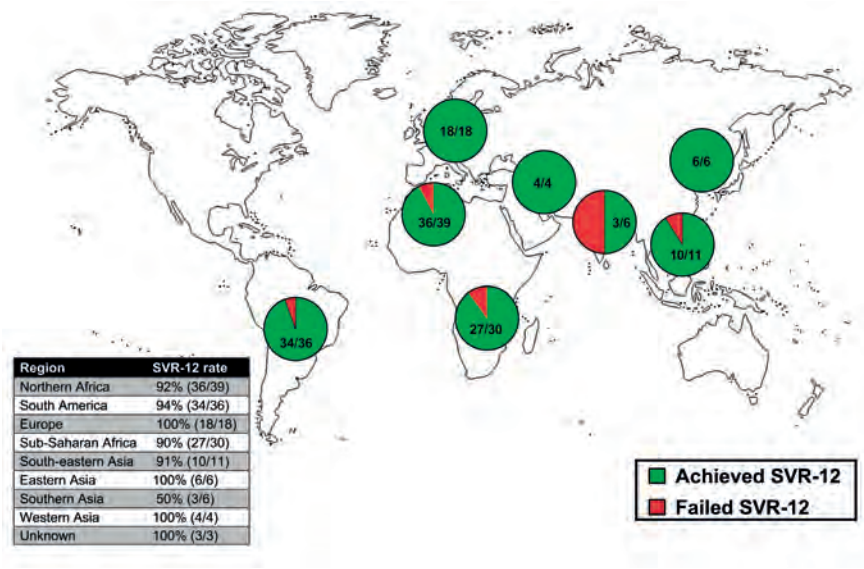

Fig. 2. SVR-12 rate per region
SVR-12: Sustained Virological Response twelve weeks after cessation of treatment.

Resistance-associated substitutions

Baseline NS5A and NS5B RAS sequences were obtained for 69 and 28 patients, respectively (Tables 4 and 5). Prevalent NS5A RAS in the sequenced non-epidemic genotypes were 24S for genotype 2, 30K and 31M for genotype 3, and 30R and 58P for genotype 4. Only one sample contained RAS at position 93, which was a successfully treated subtype 4n infection with Y93C. Regarding the NS5B region, none of the samples contained RAS at the main resistance harboring NS5B positions 150, 159, 282, or 321.

Table 3. Characteristics of the twelve patients failing DAA therapy

Genotype	Country of origin	Cirrhosis	Failed DAA regimen(s)	Successful re-treatment	Baseline RAS	Post-treatment RAS
2	Guinea	CP-A	SOF+rbv 16w	SOF/DAC+rbv 12w	NS5A: 24S NS5B: none	NS5A: 24S NS5B: none
2 clade I	Suriname	No	SOF+rbv 12w, SOF+rbv 24w, SOF/DAC+rbv 12w	SOF/GLE/PIB 16w	NS5A: 24S, 31M, 92S NS5B: none	Before & after SOF/DAC failure: NS5A: 24S, 31M, 92S NS5B: none
2i	Morocco	No[a]	SOF+rbv 12w	SOF/LDV+rbv 24w	NS5A: 24S, 31M NS5B: None	NA
2f	Guyana	No	SOF/DAC 12w	No re-treatment	NA	NS5A: 24S, 31M NS5B: None
3b	Myanmar	No	SOF/VEL 12w	SOF/GLE/PIB 16w	NA	NS5A: 30K, 31M NS5B: None
3b	Pakistan	No	SOF/DAC 12w	SOF/GLE/PIB+rbv 16w	NA	NS5A: 30K, 31M NS5B: None
3b	Pakistan	CP-A	SOF/DAC+rbv 24w	SOF/VEL/VOX 12w	NS5A: NA NS5B: none	NS5A: 30K, 31M NS5B: 159F
4k	Rwanda	No	SOF/LDV 12w	SOF/VEL/VOX 12w	NA	NA
4n	Egypt	CP-A	SOF/LDV+rbv 12w	SOF/SIM+rbv 24w	NS5A: 28M, 30R NS5B: NA	NS5A: 28M, 30R NS5B: NA
4n	Egypt	CP-B	SOF/SIM+rbv 24w	SOF/DAC+rbv 12w	NS5A: 30R NS5B: NA	NA
4v[b]	Burundi	No	EBR/GZR 12w	No re-treatment	NA	NA
6f	India	CP-A	EBR/GZR 12w[c]	SOF/VEL/VOX+rbv 12w	NA	NS5A: 28M, 31M NS5B: NA

SVR: sustained virological response. CP: Child-Pugh class. PEG: pegylated. IFN: interferon. rbv: ribavirin. DAA: direct-acting antiviral. SOF: sofosbuvir. DAC: daclatasvir. VEL: velpatasvir. LDV: ledipasvir. SIM: simeprevir. EBR: elbasvir. GZR: grazoprevir. GLE: glecaprevir. PIB: pibrentasvir. VOX: voxilaprevir. RAS: resistance-associated substitutions. NS: nonstructural protein. NA: not available. RAS are based on the EASL guideline[22]. [a]This patient had a detectable viral load of 38 IU/ml at SVR-12, and an undetectable viral load at SVR-24, and was thus not retreated. [b]This patient had a non-cirrhotic liver after orthotopic liver transplantation due to cirrhosis and HCC. [c]This patient was treated in a phase III study.

In all four non-epidemic genotype 2 infections that failed DAA therapy the 24S NS5A RAS was present, although from the genotype 2f sample only a post-treatment sequence was available. The 24S NS5A RAS was also present in all but one of the 17 successfully treated patients with a non-epidemic genotype 2 subtype and available baseline NS5A sequences. The 3 genotype 3b infections that did not reach SVR-12 had post-treatment 30K and 31M RAS, which are known to be dominant amino acids at these positions for genotype 3b and were also present in the five successfully treated genotype 3b infections. In one of the genotype 3b infections that failed treatment NS5B 159F RAS

Table 4. SVR-12 rate (n/n) per NS5A RAS and presence of baseline RAS per genotype

AA at NS5A RAS positions[a]	Genotype									
	1 (n=4)		2 (n=21)		3 (n=6)		4 (n=30)		6 (n=7)	
SVR-12	**n**	**100% (4/4)**	**n**	**86% (18/21)**	**n**	**100% (6/6)**	**n**	**93% (28/30)**	**n**	**100% (7/7)**
K24F			1	1/1						
K24G					1	1/1				
K24K							31	29/31	5	5/5
K24R	2	2/2								
K24Q									2	2/2
K24S	2	2/2	20	17/20	5	5/5				
M28C			1	1/1						
M28F			11	8/11					1	1/1
M28L	4	4/4	6	6/6	1	1/1	18	15/16	2	2/2
M28M					5	5/5	10	9/10	1	1/1
M28S			1	1/1						
M28V							3	3/3	3	3/3
M28F/I			1	1/1						
M28L/R			1	1/1						
Q30C							1	1/1		
Q30K			20	17/20	6	6/6				
Q30Q	1	1/1								
Q30R	2	2/2					24	22/24	3	3/3
Q30S							3	3/3	4	4/4
Q30T							3	3/3		
Q30K/R			1	1/1						
Q30G/R	1	1/1								
L31I			1	1/1						
L31L	4	4/4	4	3/4			12	11/12	7	7/7
L31M			16	14/16	6	6/6	19	18/19		
P32P	4	4/4	21	18/21	6	6/6	31	29/31	7	7/7
S38S	4	4/4	21	18/21	6	6/6	31	29/31	7	7/7
H58A							1	1/1		
H58P	4	4/4	19	17/19	5	5/5	22	22/22	4	4/4
H58S			1	1/1	1	1/1				
H58T			1	0/1			6	4/6	2	2/2
H58A/T							1	1/1	1	1/1
H58P/S							1	1/1		
E62A			1	1/1					1	1/1
E62D					3	3/3	1	1/1		
E62E					1	1/1	19	18/19	1	1/1
E62G	1	1/1								

Table 4. SVR-12 rate (n/n) per NS5A RAS and presence of baseline RAS per genotype (continued)

AA at NS5A RAS positions[a]	Genotype											
	1 (n=4)		2 (n=21)		3 (n=6)		4 (n=30)		6 (n=7)	
E62K							3	3/3		
E62L					1	1/1				
E62N			16	13/16			3	3/3		
E62Q	3	3/3					3	2/3		
E62R									1	1/1
E62S			2	2/2			1	1/1		
E62V									4	4/4
E62A/V			1	1/1						
E62D/E					1	1/1				
E62N/S			1	1/1						
E62N/T							1	1/1		
A92A	4	4/4					31	29/31	7	7/7
A92C			17	15/17						
A92E					6	6/6				
A92S			4	3/4						
Y93F	4	4/4								
Y93T									7	7/7
Y93Y			21	18/21	6	6/6	30	28/30		
Y93Y/C							1	1/1		

RAS: Resistance Associated Substitution. AA: Amino acids. [a]Reference amino acid originates from the H77 genotype 1a sequence. Analyzed subtypes (n): 1g (4), 2 unassigned (5), 2 clade I (3), 2 clade III (2), 2 clade V (1), 2c (1), 2f (2), 2i (4), 2k (1), 2o (1), 2p (1), 3b (5), 3k (1), 4unassigned (1), 4c (4), 4h (3), 4k (5), 4n (8), 4o (5), 4r (4), 4t (1), 6unassigned (1), 6a (3), 6e (3)

developed during treatment. In all seven genotype 4n infections the 30R RAS was present at baseline. In one of the two non-SVR 4n patients the 28M RAS was also demonstrated at baseline, which was found in two of the five successfully treated genotype 4n infections with available RAS data. 58T was present in seven genotype 4 NS5A sequences, all subtype 4n, of whom only five were successfully treated.

Table 5. SVR-12 rate (n/n) per NS5B RAS and presence of baseline RAS per genotype

	Genotype			
AA at NS5B RAS positions[a]		**2 (n=22)**		**3 (n=6)**
SVR-12	**n**	**86% (19/22)**	**n**	**83% (5/6)**
N142N	22	19/22	5	5/5
N142?[b]			1	0/1
E150A	11	9/11	6	5/6
E150I	1	1/1		
E150S	2	1/2		
E150T	6	6/6		
E150V	2	2/2		
L159L	22	19/22	6	5/6
Q206E			2	2/2
Q206H	1	1/1		
Q206K			4	3/4
Q206Q	14	12/14		
Q206R	7	6/7		
E237E	22	19/22	6	5/6
S282S	22	19/22	6	5/6
C289F			6	5/6
C289M	22	19/22		
L320L	22	19/22	6	5/6
V321V	22	19/22	6	5/6

RAS: Resistance Associated Substitution. AA: Amino acids. [a]Reference amino acid originates from the H77 genotype 1a sequence. [b]Position 142 was not included in this sequence. Analyzed subtypes (n): 2unassigned (5), 2 clade I (4), 2 clade III (2), 2 clade V (1), 2f (2), 2k (2), 2o (1), 2p (1), 3b (6)

DISCUSSION

In this study, we report DAA treatment outcome of 152 patients infected with a non-epidemic HCV genotype in the Netherlands. Overall, SVR-12 rate was 92%, which is reassuring as the majority of patients was treated with older DAA regimens with lower efficacy. However, only 73% (8/11) of patients with a genotype 3 infection achieved SVR-12, due to a 63% (5/8) SVR-rate in genotype 3b. Of note, in three of the successfully treated patients with either genotype 3b or 3k the intended first-line DAA regime was optimized after detection of RAS at baseline and subsequently tailored accordingly. These three patients were all treated in the same academic center, where baseline genotyping of all patients and baseline RAS analysis for non-epidemic genotype 3 infections are routinely performed.

A decreased DAA efficacy for genotype 3b will have serious implications for HCV elimination in Asia as this subtype is endemic in several countries with a high HCV prevalence, such as China, India, Myanmar, and Pakistan.[24–27] In China, the country with the highest HCV prevalence in the world,[1] genotype 3b accounts for 7% of all HCV infections.[24] A possible explanation for decreased DAA efficacy in genotype 3b could be that wild-type HCV-3b infections contain several resistance-associated amino acids in the NS5A region, most importantly 30K and 31M.[8,12] This combination is associated with decreased efficacy against all NS5A inhibitors.[12] In fact, a recently published *in vitro* study demonstrated that PIB was the only NS5A inhibitor with high antiviral activity against subtype 3b.[14]

In a real-world cohort study from Myanmar genotype 3b patients were treated with either SOF/DAC or SOF/VEL, showing favorable SVR-12 rates of 96% (115/120) and 91% (50/55), respectively.[27] Conversely, in a recent SOF/VEL phase 3 trial conducted in multiple South-eastern Asian countries only 76% (32/42) of included genotype 3b patients achieved SVR-12.[8] Likewise, another recent Asian trial reported 70% (14/20) efficacy of GLE/PIB in genotype 3b patients.[28] In both trials resistance-associated polymorphism 31M was present in all genotype 3b NS5A sequences.[8,28] Furthermore, four other Asian studies, albeit with only a small number of genotype 3b patients, showed low SVR-12 rates of 75% (9/12), 33% (2/6), 75% (3/4), and 50% (2/4).[29–32] Noteworthy, in multiple of these studies all patients were treated with GLE/PIB, implicating that despite PIB having the highest antiviral activity against subtype 3b, its effectiveness is not indisputable.[30–32] Perhaps some of the differences in efficacy could be related to ribavirin use, as in contrast to the other studies many of the Myanmar genotype 3b patients had ribavirin added to their therapy.[27] In a large Italian genotype 3 cohort a beneficial effect of ribavirin was seen

when added to SOF/DAC, or to SOF/VEL in case of cirrhosis, although the genotype 3 subtypes and origin of patients were not reported.[33]

So far, most studies reporting decreased DAA efficacy in non-epidemic HCV genotypes have focused on subtypes endemic in Sub-Saharan Africa.[7,10,11] In our study, we were not able to confirm these findings. In a London cohort with African patients a sub-optimal SVR-rate in mainly West-African non-1a/1b genotype 1 subtypes was seen,[10] whereas the mainly Egyptian genotype 1 infections in our cohort were all successfully treated. Likewise, all five patients in our cohort infected with the 4r subtype were successfully treated, despite that in four out of five baseline NS5A RAS were present (28V/M, 30R, 58P). Besides the low number of included patients, differences in used treatment regimens are likely to have contributed to differences between cohorts, given the fact that VEL and PIB have better in vitro antiviral activity against known NS5A RAS.[12,14]

Our study has several limitations. In particular, the inclusion of some (sub)types is limited due to the low prevalence of these genotypes in the Netherlands. Also, as we report real-world data spanning multiple years, a variety of 10 different DAA regimens was used including older regimens such as SOF + ribavirin, which had a low SVR-12 rate of 79% in our cohort. Furthermore, due to limited availability of stored samples, we were not able to obtain baseline and post-treatment RAS sequences for all patients who failed DAA therapy. However, to our knowledge, our study is the first study that aimed to evaluate DAA efficacy of all non-epidemic HCV genotypes in a country or region. Moreover, for the first time DAA efficacy in unassigned genotype 2 clades prevalent in Suriname has been assessed. As these HCV subtypes have reached Suriname and the Caribbean area through historic slave trade from Western Africa,[23] one could argue that these are in fact distinct Sub-Saharan African subtypes. Furthermore, an important strength of our study is the reliable method of genotype determination, which allows for accurate classification of subtypes. By contrast, the widely used commercial assay INNO-LiPa frequently fails to report accurate subtypes for genotype 2, 4, and 6, with rates of 51%, 5.8%, and 9.3% respectively.[13]

Our results show that despite availability of pangenotypic DAA, genotyping remains necessary for patients originating from countries where non-epidemic genotypes are present. Furthermore, in order to advance global HCV elimination, and not only HCV elimination in high-income countries, we believe that more studies reliably assessing the unique prevalence of HCV subtypes for each region of LMIC are needed, preferably including RAS analysis. It is important that these studies are conducted at a regional level, as genotype distribution can vary strongly between various regions in a country. For example, a review of 26 genotype distribution studies from several regions of

Pakistan reported a wide range of 0.2-22.3% for genotype 3b prevalence.[26] Alongside the local availability of DAA, these data should be used to develop tailored regional HCV treatment guidelines taking baseline RAS into account. We believe that, given the prevalence of baseline RAS and low SVR-12 rates in genotype 3b, SOF/VEL/VOX or SOF/GLE/PIB as first-line treatment as well as the standard addition of ribavirin should be investigated. Importantly, this would require accelerated low-price access to the most recent NS5A inhibitor DAA regimes in low-income countries.

In conclusion, DAA treatment results in most non-epidemic genotypes in the Netherlands seem reassuring. However, the low SVR-12 rate in genotype 3b infections is alarming, especially as this genotype is common in several countries with high HCV prevalence. Alongside earlier published results, these results indicate that one of the remaining challenges for global HCV elimination is confirmation and monitoring of DAA treatment effectiveness in non-epidemic genotypes.

DECLARATION OF INTEREST

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Supplementary material belonging to this chapter is available online.

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CHAPTER 10

SHOULD WE CONTINUE SURVEILLANCE FOR HEPATOCELLULAR CARCINOMA AND GASTROESOPHAGEAL VARICES IN PATIENTS WITH CIRRHOSIS AND CURED HCV INFECTION?

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ABSTRACT

Hepatocellular carcinoma (HCC) and variceal bleeding are among the most common causes of liver-related mortality in patients with hepatitis C virus (HCV)-induced cirrhosis. Current guidelines recommend HCC and gastroesophageal varices (GEV) surveillance in patients with HCV infection and cirrhosis. However, since the recent introduction of direct-acting antivirals, most patients with cirrhosis are now cured of their chronic HCV infection. As virological cure is considered to substantially reduce the risk of cirrhosis-related complications, this review discusses the current literature concerning the surveillance of HCC and GEV in patients with HCV-induced cirrhosis with a focus on the setting following sustained virological response.

GENERAL INTRODUCTION

Hepatitis C virus (HCV) infection is a major global health problem. In 2019, approximately 58 million people were chronically infected worldwide, and their overall survival is substantially impaired.[1,2] This mainly results from the progressive development of hepatic fibrosis, due to the presence of chronic hepatitis, which may result in cirrhosis. At this universal end-stage of chronic liver disease, patients are at risk of clinical complications such as hepatocellular carcinoma (HCC) and variceal bleeding.[3–5] Therefore, surveillance and primary prophylaxis strategies have been developed to optimize patient outcomes. In case of HCV eradication, patients have shown an improved clinical course.[6] In the past, PEG-interferon and ribavirin combination therapy was used. For patients with cirrhosis, this resulted in sustained virological response (SVR) rates of, on average, 30% for genotype 1/4 and 50% for genotype 2/3.[7] Nowadays, two to three months of therapy with direct-acting antivirals (DAAs) results in SVR in >95% of patients with compensated liver disease and ~80% of those with decompensated cirrhosis, with minimal side effects.[8] The general risk of post-SVR liver-related complications increases now that DAAs are more often used in patients with more advanced liver disease. Therefore, the optimal management of patients with cirrhosis and cured HCV infection should be evaluated as studies with prolonged follow-up after DAA-induced SVR are surfacing.

Hepatocellular carcinoma

Based on older natural history studies, the annual risk of HCC among patients with cirrhosis and ongoing HCV infection ranges from 3 to 7%.[9,10] The incidence of HCV-related HCC has increased over the recent decades, and the peak of HCV-related cirrhosis still lies ahead of us.[11,12] If not diagnosed at an early stage, HCC has an extremely poor 5-year survival.[13] A recent Swedish national cohort including over 3000 patients with HCC demonstrated median survival rates of 4.6 years following resection, 3.1 years after ablation, 1.4 years after trans-arterial chemoembolization, 0.5 years with sorafenib and 0.3 years with best supportive care.[14] Those who qualified for liver transplantation had the best outcome with 75% survival at 5 years. Although high-level evidence is absent, HCC surveillance in patients with HCV-related cirrhosis is therefore currently advised to detect HCC early, when curative therapy (i.e. resection, ablation or liver transplantation) is still possible.[3,4]

Detection of HCC

Current guidelines recommend HCC surveillance using abdominal ultrasound (US) as imaging modality.[3,4] Although safe and inexpensive, the operator-dependent accuracy of US is a disadvantage. Furthermore, especially in patients with a nodular transformed cirrhotic liver it can be difficult to distinguish small malignant lesions from benign

histological changes (e.g. regenerative nodules). A recent meta-analysis including 13,367 patients with cirrhosis indicated that the sensitivity of US for HCC of any stage was 84%. However, US was found to be less accurate for the detection of early HCC, with a sensitivity of only 47%.[15] The addition of alpha-fetoprotein (AFP) (at a frequently used cut-off of 20 ng/mL) to US improves the sensitivity to detect HCC in a curative stage compared with US alone (63% vs. 45%, respectively).[15] However, false-positively elevated AFP levels due to HCV-induced inflammation reduce surveillance specificity.[15,16] Therefore, current guidelines are not conclusive about the value of adding AFP in HCC surveillance.[3,4]

Computed tomography (CT) is not advised as general HCC surveillance strategy. While an improved sensitivity of CT over US for HCC detection is debated, additional downsides include potential contrast-induced nephrotoxicity and repetitive radiation exposure.[17] Magnetic resonance imaging (MRI) is time-consuming and associated with higher costs. Nevertheless, in a prospective study among 407 patients with a high annual risk of HCC (>5%), MRI did show a significantly higher HCC detection rate (86% vs. 28%) with fewer false-positives than US.[18] Especially in case of severe steatosis, which substantially reduces the reliability of US for the detection of HCC, MRI can be considered. Prospects include shortened MRI scanning protocols, which might overcome the limited availability while preserving a high sensitivity.[19]

Efficacy of HCC surveillance in cirrhosis

A large controlled trial with cluster-randomisation showed that HCCs detected through surveillance were more frequently treated with surgical resection and these patients had a substantially better outcome than those diagnosed with HCC outside of a surveillance program.[20] However, the trial was performed over 20 years ago among Chinese patients with predominantly hepatitis B virus (HBV) infection and a median age of ~40 years. Current practices in patients with HCV-related cirrhosis in Western countries are therefore mainly based on the results of cohort studies. A pivotal meta-analysis included 15,158 patients with cirrhosis (of any aetiology) and HCC from 47 studies.[19] The 3-year survival rate of 51% following surveillance-detected HCC was significantly higher than the 3-year survival of 28% following HCC detected outside of surveillance (pooled OR 1.9, 95%CI 1.7-2.2), which remained in studies that adjusted for lead-time bias. Increasing the uptake of curative therapy for early HCC may represent a route through which the benefit of surveillance can be maximized. Whereas in a meta-analysis and a more recent cohort study 63%-71% of HCC detected through surveillance was early stage HCC, uptake of curative therapy was only 35-52%.[19,21] In multiple European cohorts the median survival after HCC diagnosis was indeed higher among those compliant with the biannual surveillance recommendation, while reducing the imaging interval to three months was

not found to be beneficial.[22–25] Still, there remains controversy regarding the clinical benefit of HCC surveillance in patients with cirrhosis, as not all cohort studies reported positive outcomes.[26] This might partly explain the low uptake of the clear surveillance recommendations in society guidelines.[27]

At present, HCC surveillance with biannual abdominal US with or without AFP is considered to be cost-effective in patients with an average annual HCC risk of 1.5%.[4] While a recent study suggested that MRI-based surveillance might be even more cost-effective among patients with a sufficiently high risk of HCC,[28] those with cirrhosis and ongoing HCV infection are already well above this threshold. However, among patients with HCV-related cirrhosis and successfully treated HCV infection this should be re-assessed as both the average HCC rate and the risk of other cirrhosis-related complications are substantially reduced by curative treatment.

Should SVR influence the surveillance strategy?

While viral eradication might not influence the performance of abdominal US for the detection of HCC in patients with HCV-related cirrhosis in the short term, this may be different for AFP due to decreased hepatic inflammation. Successful antiviral therapy was shown to reduce AFP with hardly any patients remaining above 10 ng/mL in absence of HCC.[29] Repeating prior studies on the performance of US and AFP for HCC detection following successful DAA therapy is thus relevant. Considering the impact of SVR on liver-related clinical endpoints, cost-efficacy of HCC surveillance for patients with cirrhosis after HCV eradication should be assessed separately as well. This was recently done in a Canadian modelling study, which described a strong and exponential relation between the annual HCC risk and the incremental cost-effectiveness ratios (ICER) of biannual US.[30] The ICER was estimated to be below the commonly suggested willingness to pay threshold of 50,000 Canadian dollars from an annual HCC risk of 1.3% onwards. The assumptions driving these analyses should, however, be reviewed when interpreting its results in light of other health care systems. Furthermore, several developments could have lowered the risk cut-off for cost-effective HCC surveillance post-SVR. First, the clinical efficacy of surveillance might have increased over time as improved US quality could have eased the detection of HCC, although this can be challenged by an increase in fatty liver disease.[16] Second, there are potentially more life-years to be gained following an early diagnosis due to better HCC management options today.[31] Third, two multicenter studies indicated that DAA therapy among patients with successfully treated early HCC was independently associated with a lower risk of death (adjusted HR 0.4-0.5).[32,33] Finally, future risk stratification tools could further improve the cost-efficacy of HCC surveillance.

What is the risk of HCC after SVR?

Long-term follow-up studies including patients with advanced hepatic fibrosis who were treated with interferon-based therapy indicated that the risk of HCC was reduced approximately 4-fold following SVR.[34,35] Still, successful treatment did not eliminate the HCC risk, as the annual incidence of HCC was still 1.1-1.4% depending on the background population studied.[6,36] Regarding DAAs, the first small and uncontrolled studies alarmed the field because of a high rate of HCC occurrence and recurrence after successful DAA therapy. Larger and better-designed cohort studies hereafter soon indicated that the higher HCC rate following DAAs was predominantly observed because DAAs cure patients with more advanced liver disease and inherently higher HCC risk.[37–39] Importantly, in the largest cohort study including 62,354 chronic HCV-infected patients, the HCC risk reduction with SVR was similar in those cured with DAAs (adjusted HR 0.3, 95%CI 0.2-0.4) and those cured with interferon-based therapy (adjusted HR 0.3, 95%CI 0.3-0.4).[38] Nevertheless, we should expect to encounter HCC after SVR more frequently in the upcoming years since patients with more advanced cirrhosis and higher HCC risk are now treated and cured. Based on current short-term follow-up studies, the annual HCC risk after DAA-induced SVR ranges between 1.0% and 4.3% (Table 1).[35,37-60] While the annual HCC risk did not decline sufficiently during the first 4 years after DAA-induced SVR, the long-term experience following interferon-induced SVR learned us that there was no further reduction of the annual HCC risk over 10 years of follow-up.[6,46,62]

Can non-invasive tools be used to select patients for post-SVR HCC surveillance?

While the optimal surveillance protocol might vary depending on the HCC rate, the most prudent question is whether risk stratification can reliably identify SVR patients with a negligible risk of HCC. Apart from lacking cost-efficacy, HCC surveillance might be more likely to harm such patients.[63] The harms of surveillance require more attention but include emotional distress, financial costs, and physical injuries as a result of invasive diagnostics or even treatment of false-positive nodules. Parameters most frequently associated with HCC risk after interferon-induced SVR included age, ethnicity, features of the metabolic syndrome and non-invasive markers of liver disease severity. In line, a recently developed risk model among American Veterans with HCV-related cirrhosis and SVR showed that such readily available and objective clinical parameters prior to antiviral therapy could accurately assess the risk of HCC after SVR.[58] Although the mean follow-up of two years was limited, this cohort registered 344 HCC cases among 7,689 patients with cirrhosis.

While external validation needs to be awaited before implementation in daily practice, further attention goes towards the predictive relevance of the evolution of non-invasive markers of liver disease severity following DAA-induced SVR.[46,47,62] The largest study

Table 1. Studies reporting incidence of hepatocellular carcinoma after DAA-induced SVR in patients with HCV-related advanced liver disease

Author, year	Study Design	Patients with SVR and cirrhosis (n)	Mean/median Follow-up (years)	HCC cases (n)	(Calculated) Annual HCC Incidence Rate#
Cheung 2016* [50]	Prospective	317	1.3	17	4.3%
Kanwal 2017 [39]	Retrospective	7495	1.0	139	1.8%
Mettke 2018 [56]	Prospective	158	1.3	6	2.9%
Innes 2018 [37]	Retrospective	272	1.7	12	2.5%
Romano 2018 [57]	Prospective	2497	1.4 (IQR 1.0-1.9)	31	1.0%
Ioannou 2018 [58]	Retrospective	7689	2.0	344	2.2%
Calvaruso 2018 [59]	Prospective	2140	1.2 (Range 6-24)	64	2.6%
Kozbial 2018 [60]	Retrospective	393	1.3 (IQR 0.3-3.0)	16	3.3%
Nahon 2018 [61]	Retrospective	274	1.8 (IQR 1.1-2.2)	7	1.4%
Ioannou 2019 [62]	Retrospective	7533	3.0	619	FIB-4 ≥3.25: 0.5-1.4% FIB-4 ≥3.25: 2.4-3.8%
Mariño 2019 [40]	Retrospective	1070	1.6 (IQR 1.4–1.9)	56	3.1%
Park 2019 [41]	Retrospective	1218**	1.2 (SD 0.7)	17**	1.2%
Degasperi 2019 [42]	Retrospective	546	2.1 (range 0.3–3.3)	28**	3.4% (first year)
Carrat 2019 [43]	Prospective	2329	2.8 (IQR 1.8-3.4)	166**	2.2%
Piñero 2019 [44]	Prospective	653	1.3 (IQR 0.8-1.9)	28	2.8%
Shiha 2020 [45]	Prospective	1734	2.0 (SD 0.7)	101	2.9%
Tani 2020 [53]	Retrospective	191	1.2	10	1.9% (first year)
Kanwal 2020 [46]	Retrospective	6938	2.9 (SD 0.6)	NA+	1.3-2.3%
Pons 2020 [47]	Prospective	572	2.9 (range 0.3–3.8)	25	1.5%
Degasperi 2020 [48]	Retrospective – prospective	452	3.6 (IQR 0.3-4.8)	36	2.3%
Tanaka 2020 [49]	Retrospective	390	2.5	29	3%
Alonso Lopez 2020 [51]	Observational	993	3.8 (IQR 1.1-4.4)	35	1.5%
Ogawa 2020 [52]	Observational	443	3.5	69$	2.9%
Abe 2020 [54]	Retrospective	188	3.6	19	2.9%
Tamaki 2021 [55]	Retrospective	1000	3.0	148$	3.4%

*Only patients with decompensated cirrhosis were included. **Reported number in all DAA-treated patients (not specifically those with SVR). #When the annual HCC rate was not reported, this was calculated based on the presented data. ¥Analyses performed in all DAA-treated patients (not specifically those SVR). +In the entire cohort of 18,076 patients with DAA-induced SVR there were 544 patients who were diagnosed with HCC. The adjusted hazard ratio of cirrhosis with respect to HCC was 4.2 (95%CI 3.3-5.1).$Number of HCC cases not specified for patients with cirrhosis.

Abbreviations: DAA: direct-acting antivirals. SVR: Sustained Virological Response. HCV: Hepatitis C Virus. HCC: hepatocellular carcinoma. NA: not available. IQR: interquartile range.

included 7,553 patients with cirrhosis and SVR, of whom 619 were diagnosed with HCC during a mean follow-up of 3.0 years.[62] Those with a decline in their Fibrosis-4 Index (FIB-4; score to assess hepatic fibrosis based on age, platelet count, AST and ALT) from ≥3.25 prior to treatment, which indicates a high likelihood of cirrhosis, to <3.25 at SVR showed an HCC incidence of 2.5% per year. This was far above the threshold for cost-effective surveillance. Nevertheless, it was approximately half the incidence of patients with a FIB-4 that persisted ≥3.25 (5.1%/year).[62] The annual HCC risk in patients with cirrhosis and a FIB-4 <3.25 before and after successful DAA therapy was 1.2%, which is still around the cut-off for cost-effective surveillance. While efforts continue, there is currently no validated method to identify patients with HCV-related cirrhosis and SVR who have a low enough HCC risk to omit surveillance.[51] Important to consider is that non-invasive liver disease parameters have yet to be validated following HCV eradication, so that the stage of liver disease should be assessed based on pre-treatment values. So far, the diagnostic accuracy of non-invasive tests for assessment of liver fibrosis in patients with SVR has been shown to be suboptimal.[64] To illustrate, liver stiffness measurement (LSM) with Fibroscan®, a non-invasive tool with an accurate diagnostic value for advanced fibrosis or cirrhosis in patients with ongoing HCV infection, may lower or even normalize post-SVR while additional liver biopsy frequently reveals persistent cirrhosis.[65,66] As the readily available clinical parameters may have insufficient discriminative ability to exclude patients from surveillance, it is important that novel molecular biomarkers and genetic factors are actively explored through innovative translational research.[67,68]

Portal hypertension and gastroesophageal varices

Elevation of the pressure within the mesenteric circulation (i.e. portal hypertension) as a result of cirrhosis is a multifactorial syndrome. Driving factors are increased intrahepatic vascular resistance and increased portal venous blood inflow due to splanchnic vasodilatation. Portal pressure can be estimated by measuring the hepatic venous pressure gradient (HVPG) through catheterisation of the hepatic veins. An HVPG ≥10 mmHg indicates clinically significant portal hypertension (CSPH).[5] Many of the clinical complications of cirrhosis can be attributed to portal hypertension, including the development of gastroesophageal varices (GEV). GEV are shunts between the portal and caval venous systems through which portal blood can bypass the cirrhotic liver. While ectopic varices also exist, variceal bleeding is mostly encountered in case of GEV.

In general, patients without CSPH do not have GEV.[5] However, patients with compensated cirrhosis develop *de novo* GEV at a rate of approximately 7% per year.[69–71] Progression from small to large GEV (cut-off 5 mm) is seen in about 10% each year.[71] When GEV are present, the annual variceal bleeding rate ranges between 5%-15%, and mainly depends on variceal size, presence of red wale sign (indicating thinning of the variceal wall)

and Child-Pugh class as a measure of liver disease severity.[5,69,71,72] In contrast, variceal bleeding is seldom seen in patients with an HVPG <12 mmHg.[73]

Primary prophylaxis of variceal bleeding

Variceal bleeding is a severe cirrhosis-related complication. The 6-week mortality in patients with decompensated cirrhosis is in the range of 10-25%, while mortality in patients with compensated cirrhosis is low.[5,72,74,75] Multiple randomized clinical trials have assessed the clinical efficacy of primary bleeding prophylaxis in patients with high-risk GEV. Both non-selective beta-blockers (NSBB) and endoscopic band ligation (EBL) are effective methods to reduce bleeding incidence (RR 0.6 and 0.4, respectively, when compared with no prophylaxis).[76,77] Both primary prophylaxis strategies also improved all-cause mortality (RR 0.55-0.85 [76,77]) as most important clinical endpoint. Direct comparison between both primary prophylaxis strategies does not show differences in all-cause mortality.[78] Therefore, the type of primary prophylaxis should be an individual consideration based on local possibilities, patient preferences, contraindications and adverse events.[5] In contrast, secondary prophylaxis after a bleeding episode necessitates combined NSBB and EBL treatment.[5]

The high mortality of variceal bleeding and effective bleeding prophylaxis justify endoscopic monitoring of the development of GEV, which is thus recommended for patients with cirrhosis.[5] In recent years, research efforts have focussed on sparing redundant endoscopies. This has led to establishment of the Baveno criteria.[5] These indicate that screening can be safely omitted in patients with ongoing HCV infection in case of a LSM value <20 kPa and a platelet count >150x10^9/L,[5] as these patients have a low probability of high-risk (i.e. large) GEV. Applying these criteria saves approximately 26% of endoscopies, at the cost of missing only 3% of large GEV.[79] Although small GEV are missed in a larger proportion of patients, these have a low bleeding risk. Moreover, as there is no data supporting the efficacy of primary bleeding prophylaxis in small GEV, this is not recommended by current guidelines.[5] Important to consider, is that most data on portal hypertension and GEV originate from a clinical setting in which there is an ongoing etiological cause of liver disease.

Does clinically significant portal hypertension resolve after SVR?

Successful interferon-based treatment in patients with HCV-related cirrhosis reduces the HVPG and decreases long-term risk of GEV development.[80–82] Data regarding the effect of DAA-based HCV eradication were mostly limited to studies reporting short-term post-treatment HVPG measurements (Supplementary table 1).[83–87] However, prior long-term observations regarding the platelet count, as an alternative non-invasive marker of portal pressure with the possibility of repeated measurements, indicated an ongoing

amelioration over the years after interferon-based SVR among patients with cirrhosis.[88] Importantly, the main HVPG study including 226 DAA-treated patients with CSPH recently reported their 2-year follow-up results. CSPH prevalence dropped to 78% at 24 weeks post-SVR and further decreased to 53%-65% at 96 weeks.[86] Still, as many as 17% of the patients in this prospective study showed an HVPG increase at 24 weeks following cessation of successful DAA treatment.[89] Along with previous decompensation, a high baseline HVPG was independently associated with the persistence of CSPH following HCV eradication. Indeed, 2 years after successful antiviral therapy CSPH remained in 93% of patients with a baseline HVPG ≥16 mmHg versus 40% in those with a baseline HVPG <16 mmHg ($p<0.01$). This finding is supported by a prior paired HVPG measurement study [87] and might explain the lack of a clear improvement in clinical outcome following SVR in patients with decompensated HCV-related cirrhosis.[8] More studies with longer follow-up in larger numbers of patients are needed to further elucidate the long-term effects of HCV eradication on the HVPG, which remains one of the best validated surrogate markers for clinical outcome in hepatology.

Are GEV developing in patients with HCV-related cirrhosis after SVR?

As follow-up of patients cured with DAAs extends, more data concerning their effect on the development of GEV is emerging (Supplementary table 2).[90–96] In a large French cohort including 246 patients with Child-Pugh A cirrhosis due to chronic viral hepatitis (70% HCV), the cumulative rates of *de novo* large GEV at 1, 3 and 5 years after SVR were 2%, 4% and 4%, respectively.[92] In contrast, incidences of *de novo* small or large GEV following viral eradication varied between 9% and 13% after 18 to 36 months of follow-up in three smaller studies, each including approximately 60 patients with cirrhosis.[93,95,96] Among 176 patients with Child-Pugh A cirrhosis who used a maximum tolerable NSBB dosage following ligation of their GEV, the reported recurrence of GEV (size not reported) following DAA-based HCV eradication was 30% after 4 years.[94] Estimates of post-SVR progression of pre-existing small GEV to large GEV ranged from 16-62%.[91–93,95] Several factors might explain this wide range. First, there are differences in baseline liver disease severity. Factors associated with development of GEV included a platelet count $<100x10^9$/L, higher LSM value and increased spleen size, which all indicate higher portal pressure.[92,93] Second, there might be differences in the presence of the metabolic syndrome and alcohol abuse, even though the first small and likely underpowered studies could not relate these comorbidities favouring liver disease progression to post-SVR GEV development.[92,93] Lastly, results might be influenced by differences in the interval between baseline endoscopy and DAA-initiation, and random variation due to small sample sizes. More data from larger cohorts are required to identify clear risk factors and more precise incidence rates. A positive result at the other end of the spectrum is the regression of pre-existing GEV in up to 22% of patients after 2 to 3 years

following HCV eradication.[91,94] Nevertheless, for now, it seems apparent that endoscopic surveillance cannot be generally omitted in patients with HCV-induced cirrhosis and SVR.

Can non-invasive tools be used to select patients for post-SVR varices surveillance?

In line with reports that found persistent biopsy-proven cirrhosis in patients with normalized LSM values after SVR,[65,66] correlation between post-SVR LSM and portal pressure is limited.[86,97] In the main study reporting HVPG results of 226 patients with baseline CSPH successfully treated for HCV, post-SVR LSM cut-offs of <13.6 kPa and ≥21 kPa had moderate diagnostic value for the persistence of post-SVR CSPH.[86] Hence, the correlation between LSM alone and GEV development appears to be far from excellent and insufficiently reliable in clinical practice. Another surrogate marker for portal pressure is spleen stiffness measurement,[98] however more data are needed in patients with HCV-induced cirrhosis to determine its value in post-SVR follow-up.

Recently, several studies have validated the Baveno criteria in the setting of HCV eradication.[92,93,96] In a cohort of 246 cases with HBV- or HCV-related cirrhosis (70% HCV), 28% of patients had a favourable Baveno status at the time of viral suppression and none of them harboured large GEV at 1, 3 and 5 years follow-up, compared with 3%, 8% and 8% of those with an unfavourable Baveno status.[92] In case of LSM >20 kPa and platelet count <150x10^9/L, the number needed to surveil to detect one patient with high-risk GEV in 5 years would thus be 13. In this study, however, *de novo* small GEV were not considered, while these might be a precursor of large GEV. Furthermore, patients with Child-Pugh B/C cirrhosis or prior decompensation were excluded, while these have the highest risk of disease progression despite SVR. Among HCV patients with an unfavourable Baveno status prior to DAAs, Baveno status became favourable in 29% after SVR and none of these patients showed progression of GEV. In comparison, large GEV developed in 12% of those in whom the Baveno status remained unfavourable.[92] Another study confirmed the negative predictive value (NPV) of 100% for high-risk GEV in case of favourable Baveno status post-SVR, although only 15% fulfilled the criteria for a favourable Baveno status.[93] Extending the criteria to a platelet count <110x10^9/L and LSM value ≥25 kPa (also known as the expanded Baveno criteria) increased the proportion of patients with favourable Baveno status to 38%, at the cost of a decline of the NPV to 91%. In summary, also following HCV eradication, the Baveno criteria remain a reliable tool to determine the need for GEV surveillance. Evidently, however, the clinical implication of GEV following HCV eradication is contingent on the incidence and implications of post-SVR variceal bleeding.

What is the risk of variceal bleeding after SVR?

Achieving SVR has been related to a reduced risk of variceal bleeding in patients with advanced liver disease.[35,99] Indeed, although GEV progression is often reported, variceal bleeding after DAA-based HCV eradication appears to be rare within the first years, especially in patients without GEV prior to antiviral therapy (Table 2).[47,86,87,90,96,99–101] The average bleeding rate from four prospective studies (including a total of 1323 patients with HCV-related cirrhosis) was 1% after a follow-up of approximately 3 years following SVR.[47,86,87,101] One of these studies reported no bleeding in patients with favourable expanded Baveno criteria (39% of the cohort).[101] Importantly, most of these studies excluded patients with a history of hepatic decompensation or HCC, as well as individuals with HBV co-infection. In a large retrospective analysis from the Veteran Affairs hospitals in the USA, with a mean follow-up of 3 years, the incidence rate of variceal bleeding was as low as 0.2 per 100 patient-years in patients with cirrhosis without GEV prior to DAAs.[99] This is remarkably low, especially considering the almost exclusively male study population with a high prevalence of comorbidities associated with progressive liver fibrosis. As expected, in patients with pre-existing varices variceal bleeding was more frequent, with incidence rates of 4 and 13 per 100 patient-years depending on whether the patient experienced a prior bleeding episode.[99] Other factors associated with an increased risk of variceal bleeding following SVR in this study were previous ascites, spontaneous bacterial peritonitis and a platelet count <150x10^9/L, while obesity was not.[99] To consider, however, is that the low incidence of variceal bleeding could be due to adequate primary prophylaxis, even though population-based studies indicated that the compliance with guideline recommendations on endoscopic surveillance is far from optimal.[102,103]

CONCLUSION

While virological cure reduces the risk of HCC and variceal bleeding in patients with HCV-related cirrhosis, their risk of these complications is not entirely eradicated with SVR. As our experience following DAA-induced SVR in patients with cirrhosis increases, we will learn how to improve their management including the optimization of surveillance strategies for HCC and GEV. For now, the average risk of HCC in patients with cirrhosis post-SVR appears to remain high enough to justify continued surveillance (Figure 1). As sufficiently validated prognostic tools to accurately identify patients with a low risk of HCC are not yet available, all patients with HCV-related cirrhosis should currently remain included in HCC surveillance programs irrespective of successful DAA therapy or improved non-invasive parameters of liver disease severity. Future research could result in a more tailored approach. A crucial precondition, however, is that patients are able to undergo HCC treatment with reasonable expectation of clinical benefit. This should thus be repetitively evaluated during the follow-up for each patient.

Table 2. Studies reporting incidence of variceal bleeding after DAA-induced SVR in patients with HCV-related advanced liver disease

Author, year	Study Design	Patients with SVR and cirrhosis (n)	Varices at baseline endoscopy* (no / SV / LV)	Previous variceal bleeding	BL CP-score (% A/B/C)	Mean/median follow-up (years)	Variceal bleeding post-SVR	Bleeding incidence stratified for pre-treatment presence of varices
Romano 2018 [100]	Retrospective	37, decompensated cirrhosis	n.r.	35%	Median 7 (IQR 5-11)	1.0	2 (8%)	n.r.
Abadia 2019 [90]	Prospective	33	0 / 7 / 26	4 (12%)	76% / 24% / 0%	1.3 (IQR 1.2 – 1.7)	1 (3%)	Bleeding occurred in patient without prior bleeding
Moon 2019 [99]	Retrospective	7927	23% with varices, size n.r.	5%	n.r.	3.1	5% of patients with cirrhosis. Rate 1.6 per 100 patients years	No varices: 0.2 per 100 patient years Prior varices, no bleeding: 4 per 100 patient years Prior bleeding varices: 13 per 100 patient years
Mandorfer 2020 [87]	Prospective	90, BL HVPG≥6 mmHg	57 / 17 / 16	n.r.	72% / 28% / 0%	2.9	n = 1 (1%)	n.r.
Lens 2020 [86]	Prospective	226, BL HVPG≥10 mmHg	69 / 89 / 68	26	79% / 21% / 0%	3.7 (IQR 3.0 – 3.8)	n = 3 (1%)	n.r.
Pons 2020 [47]	Prospective	572	168 / 89 / 34	0	All CP-A	2.9 (range 0.3-3.8)	n = 2 (0.3%)	n.r.
Giannini 2020 [96]	Prospective	56	33 / 16 / 7	n.r.	n.r.	n.r.	0	
Corma-Gomez 2020 [101]	Prospective	435	SV or no varices: n.r. LV: 62	13	94% CP-A	3.7 (IQR 2.5 – 4.1)	n=10 (2%), 0.8 per 100 patient years	No prior bleeding varices: 0.6 per 100 patient years Prior bleeding varices: 3/13 (23%)

*Small varices defined as <5mm or Paquet grade F1. Large varices defined as ≥5 mm or Paquet grade F2 or F3. Abbreviations: DAA: Direct-acting Antivirals. SVR: Sustained Virological Response. HCV: Hepatitis C Virus. SV: Small Varices. LV: Large Varices. BL: Baseline. CP: Child-Pugh. N.r.: not reported. IQR: interquartile range. HVPG: Hepatic Venous Pressure Gradient.

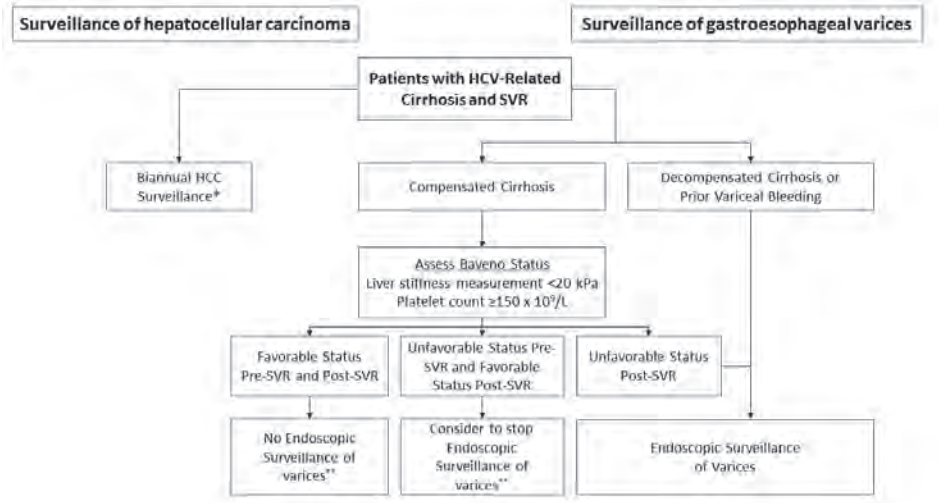

Figure 1. Decisional flowchart for surveillance of hepatocellular carcinoma and gastroesophageal varices in patients with cirrhosis and cured HCV infection.
*Consider to omit HCC surveillance in case of patients who are not expected to be able to undergo HCC treatment with reasonable expectation of clinical benefit. **In absence of signs of further progression of liver fibrosis. HCV: hepatitis C virus. SVR: sustained virological response. HCC: hepatocellular carcinoma.

In contrast, endoscopic surveillance can be prevented in a substantial proportion of patients with compensated cirrhosis and SVR by applying the Baveno criteria (Figure 1). In absence of signs of progression of liver disease, relevant GEV are indeed highly unlikely among patients with normal platelets and a LSM <20 kPa. This includes patients in whom these parameters were unfavourable prior to DAAs. In fact, as variceal bleeding after SVR seems uncommon and first variceal bleeding is associated with low mortality in case of compensated cirrhosis, future studies should elaborate on the clinical efficacy and cost-effectiveness of regular endoscopic follow-up following HCV eradication. Using the expanded Baveno criteria to further reduce the number of endoscopies might be considered. Importantly, the proportion of patients with a favourable Baveno status is at least likely to increase with time after SVR, as remodelling of the liver is a gradual process with an ongoing decrease of portal pressure. Of note, this process may be challenged by additional etiological causes of liver disease, of which metabolic syndrome and alcohol use are most prevalent. Further long-term follow-up data in patients with cirrhosis and SVR, also addressing co-factors and the evolution of liver disease parameters over time, are needed to establish optimal surveillance policies after HCV eradication.

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CHAPTER 11

THE NETHERLANDS IS ON TRACK TO MEET THE WORLD HEALTH ORGANIZATION HEPATITIS C ELIMINATION TARGETS BY 2030

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ABSTRACT

Background

The Netherlands strives for hepatitis C virus (HCV) elimination, in accordance with the World Health Organization targets. An accurate estimate when HCV elimination will be reached is elusive. We have embarked on a nationwide HCV elimination project (CELINE) that allowed us to harvest detailed data on the Dutch HCV epidemic. This study aims to provide a well-supported timeline towards HCV elimination in The Netherlands.

Methods

A previously published Markov model was used, adopting published data and unpublished CELINE project data. Two main scenarios were devised. In the Status Quo scenario, 2020 diagnosis and treatment levels remained constant in subsequent years. In the Gradual Decline scenario, an annual decrease of 10% in both diagnoses and treatments was implemented, starting in 2020. WHO incidence target was disregarded, due to low HCV incidence in The Netherlands (≤ 5 per 100,000).

Results

Following the Status Quo and Gradual Decline scenarios, The Netherlands would meet WHO's elimination targets by 2027 and 2032, respectively. From 2015 to 2030, liver-related mortality would be reduced by 97% in the Status Quo and 93% in the Gradual Decline scenario. Compared to the Status Quo scenario, the Gradual Decline scenario would result in 12 excess cases of decompensated cirrhosis, 18 excess cases of hepatocellular carcinoma, and 20 excess cases of liver-related death from 2020–2030.

Conclusions

The Netherlands is on track to reach HCV elimination by 2030. However, it is vital that HCV elimination remains high on the agenda to ensure adequate numbers of patients are being diagnosed and treated.

INTRODUCTION

Chronic viral hepatitis, if left untreated, leads to considerable morbidity and liver-related mortality.[1] Therefore, the World Health Organization (WHO) set ambitious hepatitis B (HBV) and C virus (HCV) elimination targets in 2016. The goal is to eliminate viral hepatitis as a public health threat by 2030, which is defined by the following targets: (1) 80% reduction in incidence, (2) 65% reduction in hepatitis-related mortality, (3) 90% diagnosis coverage, and (4) 80% treatment coverage.[2] The year 2015 serves as baseline for these targets. Many countries aim to reach these goals in time and elaborate efforts have been made to monitor progress towards elimination, often using mathematical models.[3,4]

With regard to hepatitis C, it appears that only few countries are on track to meeting the WHO targets in time.[5] A recent modelling study, using the latest data on chronic HCV prevalence, and annual diagnosis and treatment levels in 45 high-income countries, suggests that only Australia, Canada, France, Germany, Iceland, Italy, Japan, Spain, Sweden, Switzerland, and the United Kingdom are currently on track.[5] Tailored HCV-specific national strategies, regional or national guidelines, national expert advisory groups and/or decentralized HCV screening likely keep these countries on a trajectory towards elimination.

The situation is different in The Netherlands. While there is a national plan that is endorsed by the Ministry of Health, the government has not allocated funds to aid its execution, and the plan itself lacks specific targets and accompanying interventions. Furthermore, The Netherlands does not yet have a nationwide hepatitis registry, complicating the ability to track our progress. However, physicians took the initiative to establish a national collaboration group (HepNed) to create the necessary infrastructure to eliminate HCV. HepNed has initiated several HCV elimination projects, such as CELINE and CAC.

CELINE, which stands for hepatitis C ELimination In The Netherlands, is a nationwide retrieval project aiming to re-engage lost to follow-up HCV patients with care.[6] The project uses laboratory and patient records dating back 15 years from virtually all hepatitis treatment centers in The Netherlands. CAC, which stands for hepatitis C Chain of Addiction Care, is a project that aims to decentralize HCV care for people visiting addiction care services, one of the few remaining risk groups for chronic HCV infection in The Netherlands, even though transmission is very low.[7] Patients in several facilities all over The Netherlands are screened and linked to care, and data is collected throughout

this process. These projects have provided us with high quality data on the current epidemiology of HCV in The Netherlands.

A recent study estimated that The Netherlands will reach the WHO HCV elimination targets by 2035.[5] However, this study did not have access to the detailed epidemiologic data yielded from recent elimination projects. A previous Dutch modelling study from the pre-DAA era investigated various strategies to reduce the future HCV disease burden.[8] Many changes from their most effective strategy have since been implemented, including unrestricted access to direct-acting antivirals (DAA). Furthermore, various efforts to achieve viral hepatitis elimination have since been initiated. The aim of the present modelling study is therefore to evaluate the current timeline towards HCV elimination in The Netherlands.

METHODS

The Model

We utilized a mathematical model developed by the Centre for Disease Analysis [4] to model the current progress towards HCV elimination as well as the effect of various interventions on HCV-associated outcomes. This model has been used extensively in various healthcare situations and countries.[9–14] Briefly, the Excel-based Markov model forecasts the future HCV-infected population and associated liver-related morbidity (decompensated cirrhosis and hepatocellular carcinoma) and mortality. The model uses an age- and gender-specific disease progression framework, previously detailed elsewhere.[9] It incorporates the WHO targets and forecasts when the country will reach these goals. Ethical approval from an institutional review board was not required for the execution of this study.

Model Base-Case Input

The model requires various parameters as base-case input (Table 1). These input parameters were based on the literature and/or consensus from expert meetings with HCV physicians and public health (modelling) experts from the National Institute for Public Health and the Environment and from Municipal Health Services, and are described in Table 1 and in detail below.

Viraemic Prevalence

The prevalence of chronic HCV infection in The Netherlands in 2016 [16] was estimated by using the workbook method, originally developed to estimate the HIV/AIDS prevalence in low endemic countries with concentrated epidemics.[18] This study estimates that 22,885 people aged 15 years and older were ever chronically infected with HCV.[16] We adjusted this prevalence to include people aged 14 years or younger (Table 1), based on the age distribution detailed elsewhere.[8]

The number of viraemic individuals in 2016 was calculated by subtracting the number of patients cured up to 2016 from the adjusted 2016 prevalence estimate. Treatment data were obtained from the GIP database, a web-based database from the Dutch National Health Care Institute that contains data on physician-prescribed medication in outpatient care.[17] Supplementary Table S1 displays (pegylated) interferon and DAA prescriptions from 2000–2016. These data reflect the annual total number of individual users, independent of treatment indication. As indications for (pegylated) interferon-based therapy expand beyond chronic HCV, we revised this data to reflect the treated and cured HCV population (Supplementary File S1 and Table S2). This resulted in an

estimated population of 12,590 cured patients, leading to a baseline of 11,057 viraemic patients in 2016 (Table 1).

HCV Incidence

The biggest influx of new HCV infections in The Netherlands is generated by first-generation migrants from HCV-endemic countries. An estimated 400 new chronic infections are introduced to The Netherlands yearly due to migration, based on annual migration statistics and published prevalence data.[19,20] The model incorporates these infections into the HCV incidence. True HCV incidence, due to active transmission, is estimated to be very low in The Netherlands. People who inject(ed) drugs (PWID) used to be a major HCV risk group in The Netherlands. However, due to the implementation of several successful harm reduction strategies, accompanied by a change in drug use culture, HCV incidence has declined.[21] After 2000, the primary risk group for HCV infection was no longer PWID, but men who have sex with men (MSM).[22,23] Nowadays, almost all acute HCV cases occur among MSM.[7] The National Institute for Public Health and the Environment data from the previous 10 years show that, on average, the annual number of acute HCV cases is 54 (range 30–67).[7] The incidence of HCV re-infection has increased over the last few years, with 26 re-infections reported in 2019 as compared to 2 in 2016.[24] A recent study suggests that the WHO HCV incidence target may be hard to reach in countries where HCV incidence is already low.[25] The authors propose an adapted incidence goal: annual incidence ≤ 5 per 100,000 people. This adapted incidence goal has already been met, both in 2016 and 2019.[7,24] We have therefore disregarded the WHO incidence goal incorporated in the model.

Number of Diagnosed Individuals

Numbers of ever-diagnosed and annually diagnosed patients were based on CELINE project data (unpublished).[6] Approximately 70% of ever-infected patients received a formal diagnosis, resulting in 3963 diagnosed but untreated people remaining at large in 2016 (Table 1). During 2016–2019, an average of 728 patients were newly diagnosed with viraemic HCV annually. This number corresponds with the number of 700 used in a similar modelling study by Hatzakis et al..[26]

Table 1. Base Case Model Inputs.

Variable	Input	Source
Size of overall population (2016)	16,890,864	United Nations [15]
Ever-infected patients with chronic HCV (up to 2016)	23,647	2016 prevalence [16], adjusted to include people <15 years old
Total number of viraemic patients (2016)	11,057	Based on the adjusted 2016 prevalence [16] and the estimated number of cured patients up to 2016
Ever-diagnosed patients (up to 2016)	16,533	CELINE data (unpublished)
Total number of diagnosed patients (2016)	3963	Based on CELINE data and the estimated number of cured patients up to 2016
Number of annual newly diagnosed patients (2016)	700	CELINE data (unpublished)
Number of annual treated patients		GIP database [17]
2016	2647	
2017	1173	
2018	988	
2019	776	
Fibrosis stage restriction (2016)	≥ F0	No treatment restrictions since 2016
Maximum age eligible for treatment (2016)	85+	No treatment restrictions since 2016
Average SVR (2016)	95%	See Supplementary File S1

Number of Treated Individuals

Treatment data were obtained from the GIP database.[17] Data on HCV therapy and cure from 2000–2015 are presented in Supplementary File S1. Prior to 2016, DAA treatment was reserved for people with advanced disease (patients with F3 fibrosis or cirrhosis, liver transplant patients or candidates, and patients with severe extrahepatic manifestations). Since November 2015, all official restrictions on DAA treatment were lifted, resulting in widely available and reimbursed HCV treatment for everyone with health insurance. Therefore, SVR was assumed to be > 95% during and after 2016. A total of 776 people were treated with DAAs in 2019 (see Supplementary Tables S2 and S3).

Model Scenarios

Our aim was to evaluate the Dutch timeline towards HCV elimination, starting in 2020. First, we intended to develop a scenario maintaining our elimination efforts on the same level as in 2019 (“Status Quo” scenario). As this might be an optimistic scenario, we also wanted to incorporate a scenario in which a yearly reduction in elimination efforts was

implemented ("Gradual Decline" scenario). We also performed a sensitivity analysis, implementing a larger reduction in elimination efforts.

During the execution of this study, Coronavirus Disease 2019 (COVID-19) emerged, leading to a serious strain on healthcare in our country with devastating effects on non-COVID care.[27,28] Therefore, we implemented a substantial decrease in elimination efforts in both scenarios. This decrease was implemented for two years, as a one-year delay was deemed too optimistic. This two-year delay in the Status Quo scenario resulted in the Two-year COVID-19 Delay scenario, whereas the delay in the Gradual Decline scenario resulted in the Post-recovery Gradual Decline Scenario. All scenarios are detailed below.

Status Quo Scenario

The annual number of treated patients peaked in 2015, just after the introduction of DAAs, but declined continuously thereafter (Supplementary Figure S1). For the Status Quo scenario, we assumed that this decline would reach its plateau in 2020. We therefore reduced the number of annual treatments with 10% as compared to 2019, and applied a similar reduction to the annual number of diagnosed patients. From 2021 onwards, these numbers were modelled to remain equal to 2020. The scenario inputs can be found in Supplementary Table S4.

Gradual Decline Scenario

In the second scenario ("Gradual Decline"), we assumed a continuous reduction of 10% per year in both the number of annual newly diagnosed and treated patients, starting in 2021. The Gradual Decline scenario model inputs can be found in Supplementary Table S5. Furthermore, a sensitivity analysis was run on this scenario, to assess the impact of a larger reduction in elimination efforts ("Sensitivity Analysis"). An annual reduction of 15% in newly diagnosed and treated patients was therefore implemented, starting in 2021. Other scenario variables were not altered. The Sensitivity Analysis model inputs can be found in Supplementary Table S6.

COVID-19 Scenarios

A recent study from the United States investigated the impact of the COVID-19 pandemic on HCV care by comparing the number of newly diagnosed patients during a three-month period before COVID-19 measures with the subsequent three months. The authors found a 42% reduction in the number of new diagnoses.[29] To model the impact of COVID-19 on HCV elimination in The Netherlands, we assumed a similar decrease in diagnosis levels and furthermore assumed that the same decrease would also apply to the number of annually treated patients. In the third scenario (Two-year COVID-19 Delay), these reductions were assumed for 2020 and 2021, and model parameters were assumed to

return to Status Quo values in 2022 and remain stable thereafter. The fourth scenario (Post-COVID Recovery Gradual Decline) assumed the same two-year delay in 2020–2021 and initial recovery in 2022, but furthermore assumed a continuous annual reduction of 10% in both newly diagnosed and treated patients from 2023 onwards. All model inputs for COVID-related scenarios can be found in Supplementary Tables S7 and S8.

RESULTS

An estimated 11,327 patients were HCV-infected in 2016, of whom 3963 were estimated to be diagnosed. Following the Status Quo scenario of 630 new diagnoses and 698 treated patients annually, the WHO targets would be met by 2027 (Table 2). The incidence target, which was disregarded due to the extremely low pre-existing incidence in The Netherlands, would be met in 2034. In the Gradual Decline scenario, in which a yearly 10% reduction in diagnoses and treatments was implemented, WHO elimination targets would be met by 2032. The incidence target would not be met. All COVID-19-related scenario outcomes are detailed in Supplementary File S2, Figures S2 and S3, and Table S9. In general, an estimated 360 patients need to be treated annually from 2020–2030 in order to meet the treatment target by 2030.

Table 2. Forecasted year of elimination with scenarios "status quo" and "gradual decline".

	Year of Elimination	
WHO's Elimination Target	**Status Quo**	**Gradual Decline**
65% reduction in liver-related mortality	2020	2021
90% of infected patients diagnosed	2027	2032
80% of eligible patients treated	2025	2027
Year of elimination	2027	2032

All scenarios had a significant impact on the number of viraemic people (see Figure 1). The Status Quo scenario reduced viraemic HCV prevalence by 71% from 2015 to 2030, while the corresponding reduction in the Gradual Decline scenario was 50%. During the same time period, liver-related mortality was reduced by 97% in the Status Quo and 93% in the Gradual Decline scenario. Outcomes regarding liver-related morbidity and mortality are shown in Figure 2. The Gradual Decline scenario resulted in 12 excess cases of decompensated cirrhosis, 18 excess cases of hepatocellular carcinoma (HCC), and 20 excess cases of liver-related death from 2020–2030, compared to the Status Quo scenario.

The sensitivity analysis showed that a 15% reduction in annual diagnoses and treatments, as opposed to the 10% implemented in the Gradual Decline scenario, pushed back the WHO elimination targets significantly (see Table 3). The incidence target was not met, comparable to the Gradual Decline scenario. Furthermore, after an initial decrease, HCV prevalence started increasing from 2028 onward. The difference in liver-related morbidity and mortality was small, with one excess case of decompensated cirrhosis, two excess cases of hepatocellular carcinoma, and one excess case of liver-related death from 2020–2030, compared to the Gradual Decline scenario.

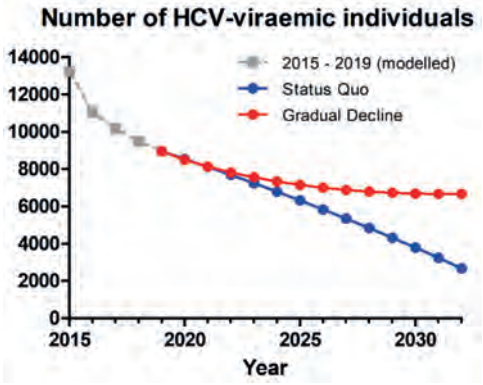

Figure 1. Predicted number of HCV-viraemic individuals in The Netherlands over time, following the Status Quo and Gradual Decline scenarios.
Abbreviations: HCV: hepatitis C virus

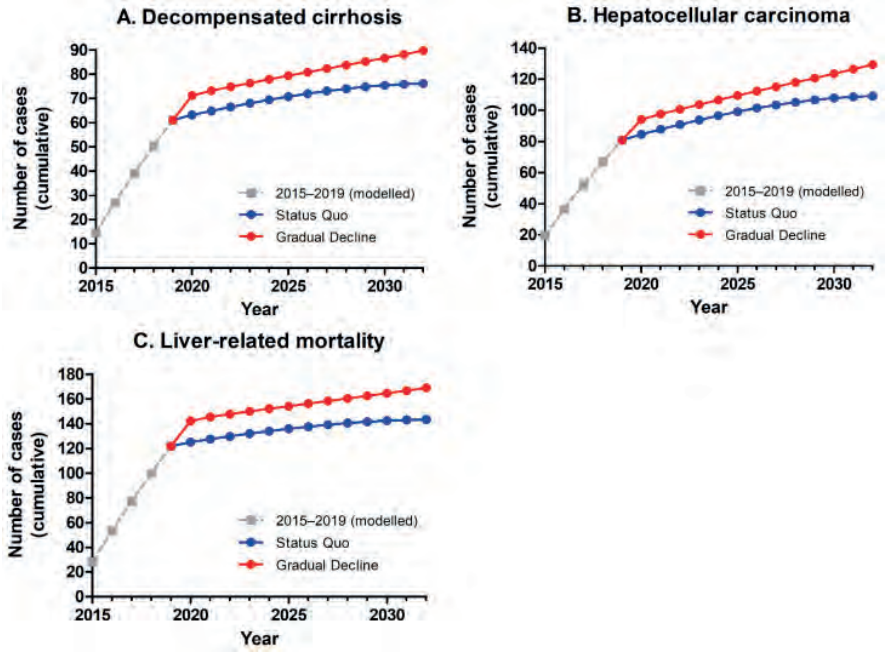

Figure 2. Predicted incident cases (cumulative) of (A) decompensated cirrhosis, (B) hepatocellular carcinoma, and (C) liver-related mortality in The Netherlands over time, following the Status Quo and Gradual Decline scenarios.

Table 3. Forecasted year of elimination in the sensitivity analysis.

WHO's Elimination Target	Year of Elimination
65% reduction in liver-related mortality	2021
90% of infected patients diagnosed	>2050
80% of eligible patients treated	2030
Year of elimination	>2050

DISCUSSION

The aim of this study was to predict when The Netherlands will meet the WHO HCV elimination targets. The results show that The Netherlands is on track to eliminate hepatitis C by 2030, if annual diagnosis and treatment rates can be maintained at 2019 levels. When an annual decrease of 10% was implemented for both diagnosis and treatment levels from 2021 onwards, WHO elimination targets were met by 2032. Both scenarios had a significant impact on viraemic prevalence and liver-related morbidity and mortality. Interestingly, the absolute numbers of incident cases of decompensated cirrhosis, hepatocellular carcinoma, and liver-related mortality sharply dropped, starting in 2020. This might be explained by the history of the HCV epidemic in The Netherlands.

The HCV epidemic took off during the heroin crisis in the 1970s, resulting in a wave of HIV and HCV infections.[21] Injecting drug use continuously decreased from 1985 to 2015, and concordantly, HIV and HCV incidence also dropped.[21] After 2000, a shift in HCV incidence from PWID to MSM was seen.[22,23] HCV infection is likely detected early in MSM due to regular testing, and treatment uptake in this group is high.[30] HCV-related morbidity and mortality in diagnosed MSM is therefore low. As most PWID have been infected from 1970–1990, the resulting peak in morbidity and mortality has most likely passed. When DAAs became available in 2014–2015, treatment was only reserved for people with F3 or F4 fibrosis. Combined with the continuous use of DAA therapy for all patients over the next few years, this may have resulted in a sharp decline in liver-related morbidity and mortality, as shown by our results. However, these modelled results need to be validated using real-life data. Hopefully, the future national HCV registry, currently in its pilot phase, will provide accurate data on HCV-related epidemiology, morbidity, and mortality.

Our results are more favourable than those of a recent study which estimated that The Netherlands would meet HCV elimination targets by 2035.[5] The authors concluded that both the 90% diagnosis coverage and the 80% treatment coverage would be the first targets to be met, in 2025, and that the 65% reduction in liver-related mortality would follow in 2035. Remarkably, our study contrasts with these results, which may have various explanations. First, the base case prevalence used in our study differed from previously published studies using this model. In the current study, we estimated the number of currently viraemic people by subtracting the number of cured patients from the ever-infected population, using a high-quality treatment database and the most recent prevalence estimate.[16,17] This led to a slightly lower base-case viraemic prevalence compared to other studies. Furthermore, due to the larger number of cured patients, it is likely that morbidity and mortality outcomes appeared more favourable compared to other studies that used different methods. A third reason, which explains

the difference regarding the treatment target, is the timing of the performed studies. As shown in Supplementary Figure S1, treatment numbers peaked after the introduction of DAAs (2015–2016) but declined shortly thereafter (2017–2019). It is possible that other, earlier studies extrapolated treatment numbers from the "peak" period, leading to an overestimation of subsequent treatment levels.

In view of the current pandemic, we modelled two scenarios projecting the impact of COVID-19. Both scenarios assumed a 42% reduction to Status Quo 2020 levels of annual diagnoses and treatments for two years, recovering to the Status Quo 2020 level in 2022. This reduction was based on a recent study from the United States,[29] as Dutch data at the time of execution of this study was lacking. However, a recently published study showed that Dutch HCV diagnoses in 2020 decreased by 43% as compared to 2019, and that the weekly relative reduction mirrored the weekly number of COVID-19 admissions.[31] Furthermore, recently published treatment data by the GIP database show that 505 people have been treated for HCV in 2020, corresponding to a 35% decrease as compared to 2019.[17] These data support the robustness of the COVID-19 scenario inputs. In the first COVID-19 scenario, diagnosis and treatment rates were kept constant after initial recovery in 2022, whereas the second assumed a 10% annual reduction from 2023 onwards. Remarkably, both scenarios resulted in earlier elimination than the Gradual Decline scenario, mainly due to the 90% diagnosis coverage target. This can be explained by the higher absolute number of new diagnoses and treatments during 2020–2030 in both COVID-19 scenarios compared to the Gradual Decline scenario. However, the number of liver-related deaths is higher for the COVID-19 scenarios (17 and 19 additional deaths, respectively, compared to the Gradual Decline scenario), which is also reflected in the year in which the 65% reduction in liver-related mortality is reached (2022 in both COVID-19 scenarios, compared to 2021 in the Gradual Decline scenario). Furthermore, both COVID-19 scenarios resulted in more cases of decompensated cirrhosis and hepatocellular carcinoma, although absolute numbers remain small.

The sensitivity analysis emphasizes the lack of flexibility in maintaining annual diagnosis and treatment levels in a low-prevalence country such as The Netherlands. A 15% reduction in these levels, as opposed to the 10% reduction in the Gradual Decline scenario, immediately resulted in the diagnosis target becoming unattainable before 2050. A 20% reduction resulted in the treatment target to be unattainable as well (results not shown). Eventually, the sensitivity analysis even resulted in an increase in viraemic HCV prevalence. This analysis therefore emphasizes the need to maintain high diagnosis and treatment levels in the upcoming years. However, maintaining high diagnosis and treatment levels may prove challenging. Unpublished data from the nationwide retrieval project (CELINE) on annual new diagnoses show a continuous decrease in the number of new diagnoses over the last five years, and GIP database data on annually treated

patients show a similar decrease. Groups in The Netherlands with the highest absolute number of (prior) chronic HCV infections are first-generation migrants from endemic countries, PWID, and people who have no (identified) risk factor for HCV infection.[16] These groups are harder to reach compared to other HCV risk groups. Fortunately, there are stakeholders in The Netherlands that aim to improve HCV care for these groups. Migrant screening, decentralization of HCV care in addiction care (CAC), and screening of prisoners are items currently high on the agenda. These efforts are vital in order to eliminate hepatitis C as a public health threat in The Netherlands. However, more support from the government is needed to enable these efforts.

Strengths and limitations

This is the first Dutch modelling study that estimates the timing of the WHO elimination targets. We incorporated the most recent, published data, as well as unpublished data that has been collected during an ongoing nationwide retrieval project (CELINE). This unpublished data has confirmed previously published data, supported expert opinion, and given new insights into the Dutch HCV epidemic, strengthening the current analysis. Four realistic scenarios were devised, resulting in a robust elimination timeline. However, this study also has several limitations.

The model is limited by the accuracy of its input parameters. Unfortunately, as country-specific data was often missing, certain assumptions had to be made. In addition, the model itself makes certain assumptions as well. The annual number of HCV drug users was approximated based on GIP database data, which incorporated various assumptions, especially for the pre-DAA era. It is possible that people have been counted more than once, due to timing of treatment, treatment duration, and possible re-treatment after initial failure or re-infection. Furthermore, the model assumes that the distribution of treatments runs concordant to the genotype distribution and is equal in all risk groups. In reality, some genotypes and/or key populations were less likely to be treated due to suboptimal treatment results or barriers to treatment. Lastly, the model does not account for different SVR percentages after re-treatment due to failure or re-infection. These assumptions may have resulted in an overestimation of the number of treated and thereby cured patients, resulting in an underestimation of viraemic prevalence. Hopefully, once the national HCV registry is established, more accurate data on epidemiology, treatment, and (long-term) clinical outcomes will be available.

CONCLUSIONS

In conclusion, The Netherlands appears to be on track to reach HCV elimination by 2030, though many challenges remain. This study demonstrates what it takes to meet the elimination targets in time, which might guide us in developing and implementing the (public) health policies that are needed. Dutch HCV elimination still needs invested stakeholders to maintain and, where necessary, improve the existing infrastructures regarding HCV care. These study results should be used as a base with which we can compare our actions in the future.

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Supplementary material belonging to this chapter is available online.

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CHAPTER 12

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

GENERAL DISCUSSION

The introduction of direct-acting antiviral (DAA) therapy, within twenty-five years of the discovery of the hepatitis C virus (HCV), is one of the most successful medical advances of the 21st century so far. With available DAA therapy, the burden of liver disease in high-income countries has been reduced at the population level, as DAA-induced sustained virological response (SVR) reduces the risk of hepatocellular carcinoma (HCC),[1,2] liver-related mortality[1–4], and all-cause mortality.[1,2,4] Hence, the era of highly effective DAA agents has brought the prospect of elimination of HCV and HCV-related complications.

In 2016, the strive towards HCV elimination was formalized by the World Health Organization (WHO), setting the ambitious goal of eliminating HCV as a public health threat by 2030.[5] At that time, approximately 71 million people were estimated to be living with HCV globally.[6] Of these, it was estimated that only 14 million (20%) were diagnosed, of whom 1.1 million people had started HCV treatment in 2015.[7] The WHO HCV elimination goals included a 65% reduction in HCV-related mortality and an 80% reduction in HCV incidence, compared to the 2015 baseline levels, as well as the targets of 90% of infections being diagnosed and 80% of eligible patients being treated.

Despite the WHO HCV elimination goals being followed by many countries presenting national hepatitis elimination plans,[8] in 2017 only 9 of 45 high-income countries were thought to be on track to meet the elimination goals by 2030.[9] For the Netherlands, it was projected in 2017 that the WHO HCV elimination goals would only be reached in 2050.[9] These projections emphasized that achieving HCV elimination remains daunting, even with the availability of DAAs. Eliminating HCV as a public health threat requires challenging steps such as reducing incidence and case-finding, linkage to care, and treatment initiation of often asymptomatic HCV patients. For low-endemic countries such as the Netherlands, micro-elimination is the favourable elimination approach, meaning that HCV elimination should be pursued within specific populations or settings with a relatively high HCV prevalence.[10]

In this thesis, remaining challenges for HCV elimination in the era of DAA agents in the Netherlands were studied, with special focus on the key populations of people living with haemophilia and people living with HIV. In the general discussion, data on current HCV epidemiology in the Netherlands are discussed, followed by remaining HCV elimination challenges for people with haemophilia and people living with HIV. Finally, policy changes that I believe to be essential to advance HCV elimination in the Netherlands are discussed.

Current HCV epidemiology in the Netherlands

The Netherlands is among the countries with the lowest prevalence of chronic HCV infection worldwide.[6] HCV prevalence estimates in the Netherlands are derived from multiple data sources representing various high-risk groups, most recently summarised in 2019.[11] In this study, prevalent ever-chronic HCV infection was defined as individuals who were alive and ever HCV-viremic, adjusted for spontaneous HCV clearance. The estimated prevalence of ever-chronic HCV infection in 2016 was 0.16%, with a low estimate of 0.06% and a high estimate of 0.27%, corresponding to approximately 23,000 individuals (low 8,000, high 38,000 individuals).[11]

For several reasons, it can be argued that in 2016 the actual prevalence of HCV-viremic individuals in the Netherlands was well below the estimate of 23,000. In **Chapter 11**, using data from a national pharmacy database, we estimated that 12,590 individuals were likely to have been cured before 2016 and thus no longer HCV-viremic. Furthermore, 60% of HCV infections in this epidemiologic overview were accounted for by first-generation migrants from HCV-endemic countries, with only 42% of the migrant population having available HCV prevalence estimates from studies in the Netherlands.[11] Therefore, for the majority of the migrant population the prevalence was based on HCV prevalence estimates from the country of origin, which is likely an overestimation.[11–13]

The CELINE study presented in **Chapter 8** provided additional insight into the epidemiology of patients ever diagnosed with HCV infection in the Netherlands. Since 85% of Dutch hepatitis treatment centres participated and HCV testing results spanning a median range of 14 years were consulted, CELINE resulted in a representative overview of the outcome of ever-diagnosed individuals in the Netherlands. The reported number of 20,183 ever-diagnosed people was an overestimation, as people diagnosed with HCV in multiple centres were registered multiple times due to privacy regulations. Nevertheless, we found that the majority of ever-diagnosed individuals had already been successfully treated, had spontaneously cleared HCV or were still in outpatient care. Only 8% were labelled as potentially having a chronic HCV infection without being linked to care and were eligible for retrieval. Furthermore, after the eligible group was invited for retrieval, 24% replied already being cured elsewhere and 14% were successfully re-linked to care. Thus, although there is a group of previously diagnosed individuals that remains to be reached, the results of CELINE indicated that the remaining HCV-viremic proportion among the ever-diagnosed HCV population is small.

CELINE used laboratory data from hepatitis treatment centres to identify individuals ever-diagnosed with HCV infection, primarily because the Netherlands lacks a central, well-covered registry of HCV patients. Only between 1999 and 2003 all HCV infections

were reported to the National Institute for Public Health and the Environment (in Dutch: "RIVM").[14] In 2003, it was then decided to remove this obligation for chronic HCV infections, and only reporting of acute HCV infections remained mandatory. Mandatory reporting of newly diagnosed chronic HCV infections was reinstated only in January 2019, leading to fifteen years of missing data. These missing data would have been crucial to inform about Dutch HCV epidemiology. Furthermore, a central registry could have been used as a source for a potentially more effective HCV retrieval effort through public health authorities rather than HCV retrieval from hepatitis treatment centres (**Chapter 8**), as has been shown in Iceland.[15] In Iceland, reporting HCV cases to the chief epidemiologist has been mandatory since 1991 and all patients are registered centrally since then.[15] Following the advent of DAAs, a national HCV elimination effort using this registry resulted in 95% of HCV infections in Iceland being diagnosed by 2018 and 92% of diagnosed individuals had started antiviral treatment.[15]

The epidemiologically most challenging population to characterize is the undiagnosed HCV-viremic population. An overview of the European Centre for Disease Prevention and Control suggested that nearly 75% of the European HCV population was undiagnosed in 2017, although a huge range between European countries was reported (3% - 96%).[16] These data did not include Dutch data, but it can nonetheless be argued that the Netherlands is more likely within the lower part of this wide range. In multiple HCV screening studies among migrant populations, the largest HCV population in the Netherlands that is assumed to be harbouring the most undiagnosed individuals, the yield rather consistently was low to moderate.[12,17–19] For example, in a population-based multi-ethnic cohort in Amsterdam, few HCV infections were found among 2500 first-generation migrants from five ethnic groups (n=2, 0.1%; prevalence in country of origin ranging from 0.6% - 1.4%)[6,20] and 500 Dutch participants (n=2, 0.4%).[12] Additionally, three of these four individuals were already linked to care for their chronic HCV infection.[12] Unless HCV screening studies in the Netherlands so far have been unable to reach the right individuals, as more healthy individuals might be more inclined to participate, this might imply that the number of undiagnosed individuals is not as high as elsewhere in Europe.[12]

Regarding HCV incidence, there is reliable epidemiological data in the Netherlands due to the long-lasting obligation to report acute HCV infection cases and due to thorough reporting of HCV data in people living with HIV as well as PWID in respectively the ATHENA cohort and the Amsterdam Cohort studies.[21–23] Taken together, these data demonstrate a low HCV incidence in the Netherlands for many years. This means that the WHO HCV elimination goal of an 80% reduction in HCV incidence compared to the already very low 2015 baseline level is hard to achieve. Therefore, an adapted incidence goal as proposed

by several authors, i.e. an annual incidence of 5 per 100,000 people,[24] should be used as an addition to this goal. In the Netherlands, this adapted incidence goal is amply met, as the number of reported acute HCV cases has been <0.5 per 100.000 for over ten years.[23]

The final aspect of HCV epidemiology, HCV-related mortality, has not been recently assessed in the Netherlands. The most recent data largely concern a period from before the era of DAA, showing a stable annual HCV-related mortality of approximately 300 individuals between 2002 and 2015[25] These data can serve as a baseline level for the WHO HCV elimination goal of a 65% reduction in HCV-related mortality compared to 2015. However, these data are insufficient to draw any conclusions on the effect of DAA. Nonetheless, as successful DAA treatment was associated with a decreased risk of all-cause mortality in several population-based cohorts in other countries after a relatively short follow-up already,[3,4] it is likely that HCV-related mortality has declined since 2015 in the Netherlands. In **Chapter 11**, we used a Markov model to estimate that the 65% reduction in liver-related mortality was already achieved in 2020 or 2021. However, the confirmation of a decreased mortality and the extent of this decrease currently remains unavailable.

Challenges for hepatitis C virus elimination in persons with haemophilia

As a result of contaminated clotting factor products, the majority of the haemophilia population was exposed to HCV before 1990, with 99% of individuals ever-treated with large pool non-HCV safe concentrate anti-HCV positive.[26] The ensuing chronic HCV infections resulted in excess morbidity and mortality among people with haemophilia. In **Chapter 2**, we reviewed the background of the viral hepatitis epidemic in this population, as well as the natural history and long-term management of hepatitis B virus (HBV) and HCV infections. Additionally, we described current procedures that ensure the safety of clotting factor products, such as donor screening, viral testing, viral inactivation procedures and use of recombinant clotting factor products. As a result of these procedures, incident HCV infections have not been reported since the early 1990s in this population in the Netherlands. Furthermore, all people with haemophilia have been systematically screened for HCV.[26] Therefore, unlike in many other HCV key populations, incident infections and case-finding are not remaining challenges for HCV elimination in the DAA era among people with haemophilia.

Previous HCV-related research in people with inherited bleeding disorders focused on the setting of ongoing HCV infection.[27–29] These studies demonstrated a high rate of liver-related complications during chronic HCV infection.[27,28] Furthermore, chronic HCV infection was independently associated with a decreased health-related quality of life (HRQoL) among people with haemophilia.[29] Fortunately, the vast majority of these

individuals in the Netherlands have currently been successfully treated for their HCV infection, as observed in a nationwide survey among people with haemophilia described in **Chapter 4** and data from the largest haemophilia treatment centre in the Netherlands reported in **Chapter 3**. Therefore, the main topic of interest regarding HCV infection in people with haemophilia currently is the follow-up after successful HCV treatment.

In **Chapter 3**, we evaluated the incidence of HCC, gastroesophageal varices bleeding and decompensated cirrhosis during chronic HCV infection, following spontaneous HCV clearance and after successful antiviral treatment. The main focus of this study was on the post-SVR setting, with 7 (4%) cases of liver-related complications occurring in 199 HCV-cured individuals, mainly incident HCC cases. We found that the incidence of post-SVR liver-related complications in people with haemophilia was higher in those cured with DAA-based regimens than those cured with interferon-based regimens. This result is in line with data from the general HCV population,[30] and most likely attributable to a longer HCV infection duration and higher prevalence of advanced fibrosis or cirrhosis in the DAA-cured group. Importantly, the incidence of hepatocellular carcinoma following successful DAA treatment in individuals with advanced fibrosis or cirrhosis exceeded the threshold of cost-effective post-SVR HCC surveillance.[31] Thus, based on the results of **Chapter 3**, we recommend continuing bi-annual HCC surveillance following HCV eradication in people with haemophilia and advanced fibrosis or cirrhosis.

In **Chapter 4**, HRQoL measured by RAND-36 questionnaires was compared between people with haemophilia either successfully treated for HCV or never chronically HCV-infected. Data from a nationwide Dutch survey conducted in 2018-2019 were used, for which all persons with haemophilia in the Netherlands were invited. Despite being successfully treated for their HCV infection, the scores of HCV-cured people with haemophilia were lower on all eight RAND-36 domains. After adjustment for confounders such as severity of haemophilia and self-reported joint impairment, differences exceeding the minimally important difference remained on seven out of eight domains. These results imply that for some persons with haemophilia, residual effects of the decades-long chronic HCV infection continue to affect their HRQoL.

Studies that evaluated pre- and post-treatment HRQoL in HCV patients successfully treated with DAA subscribe to the view that HCV eradication does not improve HRQoL in all patients. In a Dutch study with approximately 50% of participants being people with haemophilia, the only RAND-36 domain score that improved significantly between baseline and twelve weeks post-treatment was energy/fatigue.[32] Furthermore, in a large German study with real-world data of DAA-cured HCV patients without haemophilia,

approximately half of patients failed to achieve a clinically significant improvement in RAND-36 scores.[33]

The lowest RAND-36 domain scores in **Chapter 4** were observed in HCV-cured individuals with HCV infection sequelae, defined as advanced fibrosis or cirrhosis, self-reported residual symptoms of the HCV infection, or self-reported ongoing side effects of previous antiviral therapy. Nonetheless, even after excluding this group, the HCV-cured group still had lower scores on the RAND-36 domains general health, role limitations due to physical problems and role limitations due to emotional problems compared to the never HCV-infected group. Hence, based on the results of **Chapter 4**, we suggest that all HCV-cured persons with haemophilia are screened for the need for psychosocial support. Preferably, psychosocial support for HCV-cured people with haemophilia should be embedded in a general psychosocial support program within the multi-disciplinary haemophilia treatment centre, with a special focus on individuals with advanced fibrosis or cirrhosis.

Several evidence-based methods are able to improve chronic disease care if implemented, including the Chronic Care Model[34,35] and encouragement of self-management.[36] Systematically collecting patient-reported outcome measures and discussing these during annual consultations with nurse consultants should result in individualized care plans. These can be used to identify HRQoL domains that warrant further attention, for instance with peer support programs or by referring patients for an appropriate in-house or external paramedical or medical consultation.

In conclusion, HCV micro-elimination among people with haemophilia in the Netherlands is within reach. HCV incidence among people with haemophilia has been virtually absent since the early 1990s, and the remaining number of HCV-viremic individuals is low. Nonetheless, this thesis has shown that in the post-SVR setting several challenges remain for people with haemophilia. These include the post-SVR incidence of HCC and a residual impact on quality of life in some HCV-cured individuals. Especially as upcoming generations of physicians engaged in haemophilia care have not fully experienced the magnitude of the HCV epidemic in this population, awareness of these topics is important to ensure appropriate medical and psychosocial follow-up.

Challenges for hepatitis C virus elimination in people living with HIV

HCV infection is a frequent co-morbidity for people living with HIV, due to an overlap in routes of transmission and key populations. Since 1998, prospectively collected data from 98% of all people living with HIV linked to care in the Netherlands are registered in the ATHENA cohort. Thus, the coverage of the data offered by this cohort enables a

representative study of the progress towards HCV micro-elimination targets among people living with HIV in the Netherlands.

In **Chapter 5**, we used data from the ATHENA cohort to describe the prevalence of HCV RNA-positive individuals among ever HCV-tested people living with HIV in the Netherlands between 2000 and 2019. Whereas the prevalence of HCV-viremia was relatively stable between 4 to 5% from 2000 to 2015, the prevalence steeply decreased to 1.6% in 2016 and reached 0.6% at the end of 2019. This decrease in prevalence of HCV-viremic people living with HIV was coinciding with widespread uptake of DAA treatment following unrestricted access to DAA in 2015, with only 72 of 979 (7%) people living with HIV included in **Chapter 5** remaining DAA-untreated at the end of follow-up.

Nonetheless, despite the successes of a widespread DAA-uptake and a subsequent strong decrease in HCV-viremia prevalence, several challenges for HCV elimination in the DAA era remain for people living with HIV in the Netherlands. Importantly, the results of **Chapter 5** highlight incongruity with the targets that appear most challenging for HCV micro-elimination in various key populations. For men who have sex with men (MSM), DAA-uptake was very high and the remaining HCV-viremia prevalence was low. For this key population, as well as for HIV-negative MSM using HIV pre-exposure prophylaxis, reducing the incidence of primary HCV infection and HCV re-infection remains the main challenge.[21,37] While the COVID-19 pandemic initially reduced sexual risk behaviour in these groups,[38,39] limited attendance to, and delivery of, sexually transmitted infections (STIs) care reduced STI testing and might have increased the prevalence of STIs, including HCV, among MSM.[40]

For the key population of people who (formerly) inject(ed) drugs (PWID), the incidence of primary HCV infection and HCV re-infection has been very low for many years.[21] This low incidence is mainly due to harm reduction services and the high HCV-viremia baseline prevalence of 60-75% before 2014, as reported in **Chapter 5**. For the PWID key population, the main challenge for HCV elimination in the era of DAA is to increase DAA-uptake and reduce HCV-viremia prevalence. In **Chapter 5**, we report that at the end of 2019 HCV-viremia prevalence in PWID was 24 times higher than in MSM. Furthermore, belonging to the PWID key population was strongly associated with a lack of DAA-uptake. As discussed in detail later, enabling decentralized DAA treatment and integration of HCV treatment into addiction care, primary care, and mental health care might contribute to reaching the remaining DAA-untreated HCV-viremic people living with HIV in the Netherlands. Additionally, reducing HCV-viremia prevalence should be included in key population-specific HCV elimination targets for PWID.

In **Chapter 6**, data from nine observational cohorts of people living with HIV from six different high-income countries were used to compare DAA-uptake during unrestricted access between different health care settings. Several proxies for a lower engagement in HIV care were associated with a lower rate of DAA initiation, indicating that efforts to increase engagement in care and decentralized DAA care pathways are required to increase DAA-uptake among people living with HIV in high-income countries. DAA initiation rates varied across countries, with the Netherlands being among the countries with the highest DAA initiation rate. Nevertheless, differences in DAA-uptake between countries might also complicate micro-elimination efforts in the Netherlands, especially by the external introduction of HCV infections through migrants and MSM.[41,42] For MSM, it has already been shown that external introductions of HCV infection due to international transmission have recently increased.[42] Interestingly, in contrast to the national data of **Chapter 5**, belonging to the PWID key population was not associated with a lower rate of DAA initiation compared to belonging to the MSM key population in the international analysis of **Chapter 6**. In **Chapter 6,** DAA-uptake in the Netherlands was higher than the population mean for MSM but not for PWID, underlining the finding of **Chapter 5** that DAA-uptake for PWID in the Netherlands is relatively staying behind.

Another potential challenge for HCV elimination is a sub-optimal DAA efficacy for HCV subtypes endemic to Sub-Saharan Africa and Southeastern Asia. However, studies that reported on this issue hardly included individuals with HIV/HCV co-infection.[43–46] Therefore, the extent of this issue in individuals with HIV/HCV from these regions residing in Europe is unknown. This is concerning, given that HIV/HCV co-infection prevalence is high in several countries in Sub-Saharan Africa and Southeastern Asia and migrants from these regions comprise a substantial part of individuals living with HIV in Europe.[47,48] In **Chapter 7**, we report the results of a European, cross-sectional study that assessed the efficacy of interferon-free DAA among individuals with HIV/HCV originating from these regions. SVR rates similar to those observed in other HCV populations were found. This suggests that it is unlikely that sub-optimal DAA response to HCV strains from Southeastern Asia and Sub-Saharan Africa could become a major challenge for HCV elimination in individuals with HIV/HCV in Europe.

Additionally, these results allow for further consideration on the recommendation of the European Association for the Study of the Liver (EASL) that non-structural protein (NS)5B sequencing should be the standard method for baseline genotype determination in all individuals with HCV originating from Southeastern Asia or Sub-Saharan Africa.[49] In settings where these sequencing methods are not readily available, the high SVR-12 rate observed in **Chapter 7** could support the decision to omit baseline NS5B sequencing for individuals with HIV/HCV from Sub-Saharan Africa or Southeastern Asia. However,

in the Netherlands, NS5B sequencing methods are available at reasonable cost in all laboratories performing HCV genotyping. In this case, with an SVR rate around 95%, approximately one in twenty individuals could potentially benefit from a tailored DAA treatment regimen if a non-epidemic genotype were detected, and the demand for expensive DAA re-treatment could be reduced.

In conclusion, the high DAA-uptake and sharp decrease in HCV-viremia prevalence reported in **Chapter 5**, along with the previously reported decrease in the incidence of HCV primary infections and re-infections,[21] show that the Netherlands is approaching HCV micro-elimination among people living with HIV. Additionally, sub-optimal treatment efficacy does not seem to be a remaining challenge in the DAA era for individuals with HIV/HCV from Southeastern Asia or Sub-Saharan Africa living in Europe. Nevertheless, this thesis has shown that more effort is required to reduce HCV-viremia prevalence among PWID, by reducing barriers to DAA treatment uptake. Furthermore, differences in DAA-uptake between various countries might complicate HCV-elimination efforts, as external introductions due to international travel or migration from countries with a higher HCV-viremia prevalence can contribute to an ongoing epidemic.

Challenges for Hepatitis C elimination in the Netherlands

The future of HCV elimination in the Netherlands

In **Chapter 11,** we modelled the current progress towards HCV elimination in the Netherlands and translated this into the expected timing of achieving the WHO HCV elimination goals. These calculations included scenarios where the observed 43% reduction in HCV diagnoses during the COVID-19 pandemic was incorporated.[50] In the scenario of a continuous reduction of 10% per year in both the number of annual newly diagnosed and treated patients, starting in 2021, the projected year of HCV elimination was 2032. Of note, the anticipated timing of HCV elimination was not delayed due to the reduction in HCV diagnoses during the COVID-19 pandemic. Thus, these projections indicate that the Netherlands is on track to achieve the WHO HCV elimination goals shortly after the intended year of 2030. However, in a sensitivity analysis that assumed a 15% reduction in HCV diagnosis and treatment levels, HCV elimination was not reached before 2050. This emphasizes the need to maintain high HCV testing and treatment levels.

For low-endemic countries such as the Netherlands, current evidence suggests that general or birth cohort screening is not cost-effective.[17,51,52] In these countries with a low HCV prevalence, specific populations or settings with a higher HCV prevalence should be prioritized[10] Importantly, several key populations in the Netherlands have

nearly achieved HCV micro-elimination, such as people with haemophilia (**Chapter 3 and Chapter 4**) and people living with HIV (**Chapter 5**).[21] Hence, maintaining high HCV diagnosis and treatment levels requires the implementation of new micro-elimination initiatives, fundamental policy changes and sustainable funding.

Policy changes required to advance HCV elimination in the Netherlands in the era of DAA

DAA treatment outside the hospital setting

In the Netherlands, DAA agents can currently only be prescribed by hepatologists or infectious disease specialists in hospitals that are certified hepatitis treatment centres. With the availability of pangenotypic DAA regimens with few side-effects, simple laboratory-based scores for assessment of liver fibrosis, and a comprehensive drug-interaction checker, it can however be argued that HCV treatment for non-cirrhotic patients in the era of DAA no longer requires specialized care. As the negative predictive value of laboratory based-scores for assessment of liver fibrosis in the setting of non-hospital HCV care pathways is above 95%, application of these scores minimizes the risk of including cirrhotic patients in decentralized HCV care pathways.[53,54] Potential settings where decentralized DAA access could be offered to lower barriers to HCV treatment include haemophilia treatment centres, sexually transmitted disease (STD) clinics, addiction care, homeless services, or primary care.

Both **Chapter 5** and **Chapter 8** subscribe to the view that decentralized DAA access would be beneficial for HCV elimination in the Netherlands. In **Chapter 5**, infrequent visit attendance was strongly associated with lack of DAA-uptake among people living with HIV and often reported as reason for remaining DAA-untreated in in-depth questionnaires. Additionally, belonging to the key population of PWID was strongly associated with remaining DAA-untreated. The majority of DAA-untreated individuals were using opioid substitution therapy, which could be ideal to link to HCV treatment.[55] Importantly, only 10% of PWID with chronic HCV infection in the Netherlands are estimated to have an HIV/HCV co-infection.[11] For PWID without HIV, decentralized access to DAA treatment will be far more beneficial, as in contrast to individuals with HIV/HCV they are not already engaged in care with a physician currently eligible to prescribe DAAs. This thought aligns with the results of the nationwide retrieval project CELINE (**Chapter 8**), in which the vast majority of retrieved individuals belonged to the population of PWID without HIV and frequent no shows was among the most common reasons for becoming lost to follow-up. Loss to follow-up from HCV care thus seems a problem among PWID in the Netherlands and DAA treatment outside of conventional HCV care pathways may aid HCV micro-elimination in this key population.

Several studies have demonstrated the feasibility and benefit of decentralized DAA access.[55–60] A prospective multicentre study in Belgium reported high rates of screening, linkage to care and DAA initiation among PWID in an HCV care pathway integrated with addiction care.[61] In a cluster-randomized trial in Scotland, individuals receiving opioid substitution therapy had a significantly higher rate of DAA initiation and SVR-12 if allocated to a pharmacy-led, local HCV care pathway compared to conventional, hospital-based care.[55] Comparable results were observed in a randomized trial at a syringe service program in New York, where the greatest attrition in the conventional care pathway was seen at the stage of referral to the hospital and clinical visit attendance.[60] Furthermore, DAA treatment by non-specialist compared to specialist health personnel has similar SVR-12 rates and is more cost-effective.[57,58] Taken together, these programs seem highly effective and appear crucial to advancing HCV elimination in the Netherlands.

To ensure the successful implementation of decentralized DAA treatment, regionally organized and accessible HCV care pathways are required. The most feasible and economic form of these HCV networks would be coordination by nurse consultants, supervised by hepatologists or infectious disease specialists. Within these networks, counselling can be offered to physicians engaged in care with a patient with an HCV infection, and their patients. Additionally, these structures can be used to actively promote and enhance knowledge of decentralized DAA treatment. Furthermore, involved nurse consultants can collaborate with general practitioners or other health care providers to increase the yield of retrieval efforts initiated by hepatitis treatment centres, such as presented in **Chapter 8.** For lost to follow-up individuals with HCV, the possibility of initiating DAA treatment with a physician that they are already familiar with might reduce the barrier to re-linkage to HCV care. Finally, the nurse consultant can assess whether all necessary pre-treatment checks have been completed, such as assessment of liver fibrosis stage and drug-drug interactions. Making formal approval of the initiation of decentralized DAA treatment within the regional network a prerequisite for starting treatment, ensures the safety and effectiveness of decentralized HCV care pathways.

HCV screening and treatment in prisons

Systematic HCV screening and treatment in prisons is important for several reasons. First, HCV prevalence in prisoners is high. In a study assessing HCV RNA prevalence in Dutch prisons in 2009, based on consulting medical files only, the prevalence of HCV-viremic individuals in prisons was estimated to be between 2% and 8%.[62] Although data on systematic HCV screening for prisoners in the Netherlands are lacking, HCV screening studies in other European countries including Belgium consistently confirm this high HCV prevalence in prisoners.[56,63–66] Second, various studies report high uptake of HCV testing

and DAA treatment offered in a prison setting.[63,64,66] Third, HCV transmission between prisoners can occur during detention, due to risk behaviour such as unsterile tattooing, sharing needles and men who have sex with men, with limited harm reduction services during detention.[65] Treatment scale-up in prisons has been demonstrated to reduce HCV incidence in prison.[67,68] Finally, the prison setting could serve as an ideal setting to reach HCV patients who are difficult to engage in regular health care. In the retrieval study in **Chapter 8**, detention was frequently encountered as a contributing factor to becoming lost to follow-up from HCV care.

Although HCV testing and treatment are not prohibited for prisoners in the Netherlands, testing and treatment rates are low as systematic screening lacks. Moreover, efforts to set up micro-elimination projects in the prison have so far been withheld by the Custodial Institutions Agency (in Dutch: 'Dienst Justitiële Inrichtingen').[69] The reason for the reluctance of this governmental body is that Dutch prison healthcare is financed by the Ministry of Justice and reimbursing DAA treatment would require a substantial part of their healthcare budget.[69] Although HCV testing and treatment scale-up in prisons is cost-effective, even at DAA prices that are now historical,[70] the Ministry of Justice does not directly profit from this long-term cost-effectiveness. Hence, an innovative and interdepartmental strategy for funding is required to facilitate comprehensive HCV care pathways in the prison setting. Due to the current lack thereof, HCV micro-elimination in the prison setting seems unlikely in the near future.

Systematic screening of migrants from HCV-endemic countries

As described in **Chapter 11**, an estimated 400 individuals with chronic HCV infection are migrating from HCV-endemic countries to the Netherlands on a yearly base. Hence, migration impacts the number of HCV-viremic individuals and therewith potentially increases HCV-related morbidity and mortality in the Netherlands. This issue is recognized by the EASL, who recommend screening and treatment for viral hepatitis at the port of arrival for immigrants and refugees.[71] A cost-effectiveness analysis conducted in the Netherlands assessed that HCV screening was cost-effective for migrants from countries with an HCV RNA prevalence ≥0.22%, even with historical DAA prices of approximately double the current prices.[72]

Nonetheless, only compulsory tuberculosis screening is currently required for immigrants in the Netherlands, given that they are migrating from a country with a high tuberculosis incidence. In a pilot study conducted between 2013 and 2015, voluntary HBV and HCV screening was offered during this routine tuberculosis entry.[73] With 54% screening uptake, 2.2% HBsAg-positivity and 1.1% anti-HCV positivity (HCV RNA results not reported for all), the yield of this screening was moderate but substantial. The yield

could be further increased by increasing screening uptake through opt-out screening and by disconnecting viral hepatitis testing from tuberculosis testing indications, as only 55% and 13% of screened migrants in this study originated from HBV- or HCV-endemic countries, respectively.[73]

A more challenging migrant population to target at entry are migrants from countries in the European Union, as these individuals are not registered on arrival. However, there are opportunities to target these individuals too, as registration in the municipality of residence is required for a stay exceeding three months. For means of HCV elimination, this is especially interesting for migrants from Eastern Europe. Eastern European countries are among the countries with the highest net migration rate in the Netherlands[74] as well as among the countries with the highest HCV prevalence in the world.[6,75] Dutch data on HCV prevalence in this migrant population is limited and only consists of studies with small sample size, that nonetheless consistently report a high HCV prevalence.[59,76,77] Special attention is currently warranted for refugees from Ukraine coming to the Netherlands, as the HCV RNA prevalence of approximately 3.1% in 2020 makes Ukraine the country with the highest HCV prevalence in Europe.[78]

An innovative approach to increase the yield of large-scale screening of migrants, especially for the geographically-spread migrants that are not registered at arrival, might be the use of self-testing methods. Saliva-based HCV tests for the detection of HCV antibodies have excellent sensitivity and specificity.[79] Interestingly, the COVID-19 pandemic has increased awareness about infectious diseases, enhanced the understanding of diagnostics, and introduced the concept and application of self-testing to a large public. Therefore, saliva-based HCV self-tests could serve as a valuable addition to centralized testing locations for HCV screening campaigns both in the migrant population as well as in other populations.

Three factors are crucial for the successful implementation of HCV screening for migrants at entry or upon municipality registration in the Netherlands. First, funding for HCV testing and treatment is critical. This requires close collaboration between governmental bodies including municipalities, public health services, the Central Agency for the Reception of Asylum Seekers (in Dutch: “COA”), funded by the Ministry of Justice, and the Ministry of Health. Second, a cost-effective analysis is needed to assess whether selection on risk factors and/or country of origin is preferable. Finally, linkage to care of migrants with HCV who move between various locations in the Netherlands is challenging and requires strict and central coordination by public health services and the Central Agency for the Reception of Asylum Seekers.

An additional challenge for HCV elimination in the DAA era that particularly concerns migrants from HCV-endemic countries in Southeastern Asia and Subsaharan Africa is that these regions harbour many region-specific HCV genotypes with naturally occurring resistance-associated nucleotide sequences.[80] These so-called non-epidemic HCV genotypes were hardly included in DAA registration trials. However, several post-registration DAA trials and real-life studies suggested a decreased efficacy of DAA treatment in some of these genotypes.[43–46] Potentially, this could hamper HCV elimination efforts in the migrant population of the Netherlands.

In **Chapter 9**, we studied DAA efficacy in patients treated for an HCV infection with a non-epidemic genotype in the Netherlands, including data from all but one of the laboratories performing HCV genotyping in the Netherlands. In general, the observed SVR-12 rate was re-assuring, with 92% (140/152) of included patients being successfully treated. Nonetheless, only 73% (8/11) of patients with a non-epidemic genotype 3 infection, either 3b or 3k, achieved SVR. This was despite three of the successfully treated patients with genotype 3 having received a tailored DAA regimen that was optimized following the detection of RAS at baseline. Fortunately, the absolute prevalence of these genotypes is most likely too low to have a large impact on HCV elimination efforts in the Netherlands. Nonetheless, even in the era of pangenotypic DAA regimens, genotyping using NS5B sequencing remains valuable to identify individuals from regions where non-epidemic genotypes are prevalent who might benefit from tailored DAA regimens. Additionally, alongside previous studies reporting a decreased DAA efficacy in non-epidemic genotypes common in parts of Southeastern Asia or Sub-Saharan Africa,[43–46] the results of **Chapter 9** demonstrate that one of the remaining challenges for global HCV elimination is to confirm and monitor DAA treatment effectiveness in non-epidemic genotypes.

Retrieval as a repeated effort

The nationwide effort to retrieve previously diagnosed but lost to follow-up HCV patients (**Chapter 8**) resulted in 219 HCV patients being re-linked to care. Especially since 28% of retrieved individuals were diagnosed with advanced fibrosis or cirrhosis, retrieval can significantly contribute to reducing HCV-related mortality. Nonetheless, approximately 50% of patients invited for retrieval were not re-linked to care as contact was not established, re-linkage to care was refused, or addiction problems complicated re-entering care. Furthermore, some retrieved patients became lost to follow-up again following re-linkage to care but before DAA treatment was initiated. Thus, a group of HCV-viremic patients who were previously diagnosed but no longer engaged in HCV care remains. For these individuals, persistence in retrieval efforts may pay off, as concluded

in a previous qualitative study including retrieved HCV patients.[81] Hence, annual or bi-annual retrieval efforts could be beneficial for HCV elimination in the Netherlands.

As retrieval is labour intensive, a lack of funding and time is a complicating factor for initiating repeated retrieval efforts. Nevertheless, for several reasons, the time investment required for repeated retrieval efforts will most likely turn out to be relatively limited. First, retrieval that is part of standard care and unlike the CELINE study in **Chapter 8** has no research purposes will bypass the need for elaborate institutional review board processes and data collection. Second, the framework laid out by CELINE and lessons learned from CELINE will increase the efficacy of retrieval. Third, future retrieval efforts will require less time as the number of patients eligible for retrieval will continue to decline. Finally, the workload can be further reduced by implementing digital innovations, such as a case-finding algorithm or electronic health-record embedded HCV testing alerts for HCV-infected people or those at risk of HCV infection.[82,83]

Adequate post-SVR follow-up for individuals with HCV-related cirrhosis

Since DAAs achieve high SVR rates in patients with cirrhosis, the etiological cause of liver fibrosis has been removed in the majority of patients with HCV-related cirrhosis who are linked to care. In the literature review presented in **Chapter 10,** we discussed whether surveillance of HCC and/or gastroesophageal varices should be continued following DAA-induced SVR. Although HCV eradication significantly reduces the risk of HCC and gastroesophageal varices bleeding in patients with HCV-related cirrhosis, this risk is not entirely eradicated with SVR. Hence, detection of HCC in an early stage and prophylactic treatment of high-risk varices continue to be of value post-SVR to reduce HCV-related mortality.

The data summarised in **Chapter 10** show that the average risk of post-SVR HCC in patients with HCV-related cirrhosis is above the threshold for cost-effective post-SVR HCC surveillance.[31] Furthermore, sufficiently validated prognostic tools to identify cirrhotic patients with a low HCC risk are currently lacking. Post-SVR HCC surveillance should therefore be offered to all patients with HCV-related cirrhosis, given that clinical benefit of early-stage HCC treatment is within reasonable expectation. Identifying reliable markers of a low risk of HCC and long-term follow-up studies to determine the duration of HCC surveillance after successful DAA treatment are important topics for future research. Regarding gastroesophageal varices, available data suggest that the risk of post-SVR variceal bleeding is very low and endoscopic surveillance can thus be safely omitted in case of compensated cirrhosis, an absence of a history of variceal bleeding, and a favourable post-SVR Baveno status (i.e. liver stiffness <20 kPa and platelet count >150 x 10^9/L).[84]

HCC and gastroesophageal varices surveillance are strictly embedded in routine care for patients with cirrhosis and an ongoing HCV infection. For individuals with HCV-related cirrhosis and successfully treated HCV infection, however, surveillance uptake is sub-optimal. Even fewer patients with advanced liver fibrosis are included in post-SVR HCC surveillance programs, despite that surveillance is indicated for this group according to the EASL guidelines.[49] Including lost to follow-up patients with HCV-related cirrhosis and successfully treated HCV infection in retrieval efforts should be considered. By increasing and monitoring post-SVR linkage to care, HCC will be detected in a curable stage more often and thus HCV-related mortality will be reduced.

Funding for HCV elimination efforts in the Netherlands

The above-mentioned policy changes appear crucial to keep on track towards HCV elimination in the Netherlands by 2030. For successful implementation of these policy changes, sustainable funding is key. Already in 2016, the Dutch national hepatitis plan stated the importance of acquiring new sources of funding from both the public and private sectors for HCV-related research and micro-elimination initiatives.[8] Nonetheless, in recent years, the funding of HCV elimination projects was largely acquired from pharmaceutical companies, whereas governmental funding has been scarce. This is undesirable and likely problematic in the near future for several reasons. First, pharmaceutical companies have been funding single micro-elimination projects, whereas sustainable funding is required for the above-mentioned policy changes. Second, compared to the large investments required for HCV elimination projects such as CELINE (**Chapter 8**), the yield has been relatively low and thus the willingness of pharmaceutical companies to continue their investments in micro-elimination efforts is waning. Third, due to the declining number of patients eligible for DAA treatment and the prospect of expiring DAA patents in the future, pharmaceutical companies are increasingly re-locating their funds and attention away from HCV elimination projects. Finally, and most importantly, it can be questioned whether the dependency on pharmaceutical companies is ethically desirable, as the primary goal of these stockholding companies is to make a profit.

Taken together, these arguments demonstrate the necessity to ensure sustainable funding for HCV elimination from public sources. Preferably, the allocation of funding should be centrally coordinated by a multidisciplinary committee including stakeholders from the National Institute for Public Health and the Environment (in Dutch: RIVM), public health services, general practitioners, hepatology, infectious diseases and medical microbiologists specialist associations. As a first step, however, these stakeholders must intensify their endeavour to increase political and societal awareness of the lack of funding.

CONCLUSION

The introduction of highly effective DAA agents has made elimination of HCV as a public health threat a feasible and desirable goal for high-income countries. Studies presented in this thesis subscribe to the view that the Netherlands is on track to achieve HCV elimination in or shortly after 2030. HCV micro-elimination is already within reach for the key populations of people with haemophilia and people living with HIV, although challenges such as post-SVR HCC incidence for cirrhotic patients and discrepancies in DAA-uptake between key populations remain. Importantly, maintaining high HCV testing and treatment rates is critical to remaining on track towards timely HCV elimination. Therefore, the policy changes proposed in this thesis together with increased political and societal awareness and governmental funding appear crucial to prevent HCV from staying a public health threat in the Netherlands.

Call for action

Based on the studies and the general discussion presented in this thesis, several recommendations that may contribute to staying on track towards the timely elimination of HCV as a public health threat in the Netherlands can be made.

Public health recommendations

- Sustainable funding from public sources is crucial to keep on track towards HCV elimination in the Netherlands. An intensified endeavour from stakeholders is required to increase political and societal awareness of the current lack of funding.
- Decentralization of DAA treatment should be enabled and encouraged to lower barriers to DAA treatment uptake. This concerns settings such as haemophilia treatment centres, STD clinics, addiction care, homeless services, and primary care. Easily accessible regional networks involving nurse consultants should be formed to coordinate and support decentralized HCV care pathways.
- Systematic HCV screening of migrants from HCV-endemic countries, including those from Eastern European countries belonging to the European Union, is crucial to limit the impact of migration on the number of HCV-viremic individuals. Successful implementation requires cooperation between various governmental bodies concerning funding and linkage to care.
- Opt-out screening for infectious diseases prevalent among imprisoned individuals, including HCV, should become standard of care in the prison setting. Successful implementation requires interdepartmental agreements between the Ministry of Justice and the Ministry of Health regarding funding. Additionally, epidemiological studies and micro-elimination projects in the Dutch prison settings need to be enabled.
- Repeated retrieval efforts of previously diagnosed but lost to follow-up individuals with HCV need to be encouraged. Decentralized DAA treatment can increase the yield of retrieval as the treatment can be prescribed by a physician the patient is familiar with. Recurrent retrieval efforts will contribute to reducing HCV-related mortality, especially since the prevalence of advanced fibrosis and cirrhosis among previously diagnosed but lost to follow-up HCV-viremic patients is high.
- Including patients with HCV-related cirrhosis and successfully treated HCV infection who are no longer engaged in HCC surveillance programs in retrieval efforts should be considered. Increasing and monitoring post-SVR linkage to care will result in HCCs being detected in a curable stage more often, and thereby reduce HCV-related mortality.
- Key population-specific HCV elimination targets should be implemented for micro-elimination purposes. Reducing HCV-viremia prevalence should be included in the HCV elimination targets, especially for people who (formerly) inject(ed) drugs.

- Confirmation and monitoring of the effectiveness of DAA for non-epidemic genotypes are important to advance HCV elimination in populations where these genotypes are common.

Recommendations for HCV care

- Awareness and knowledge of potential residual consequences of successfully treated HCV infection should be enhanced among haemophilia treatment physicians. This mainly includes the indication for post-SVR HCC surveillance for individuals with pre-treatment advanced fibrosis or cirrhosis and evaluation of the need for psychosocial support in HCV-cured individuals with haemophilia.
- Patients with HCV-related cirrhosis should be offered bi-annual HCC surveillance, irrespective of successful DAA treatment or improved non-invasive parameters of liver fibrosis following HCV eradication.
- Post-SVR endoscopic varices surveillance for patients with HCV-related cirrhosis should only be offered to patients with a history of variceal bleeding or in case of an unfavourable post-SVR Baveno status.
- Baseline HCV genotype determination using NS5B sequencing should be standard of care for HCV RNA-positive patients from Southeastern Asia or Subsaharan Africa in settings where these methods are readily available, such as the Netherlands. This allows identifying individuals with non-epidemic HCV genotypes who might benefit from tailored DAA treatment regimens.

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APPENDICES

SUMMARY IN DUTCH (NEDERLANDSE SAMENVATTING)

Introductie

Hepatitis C (HCV) is een infectieziekte veroorzaakt door een virus dat voornamelijk de lever aantast. Bij ongeveer 70 tot 80% van de personen met een HCV-besmetting kan het lichaam het virus niet vanzelf opruimen, met als gevolg een chronische HCV-infectie. De meeste mensen ervaren weinig symptomen van deze infectie. Desondanks zorgt het virus voor progressieve schade aan de lever, waardoor fibrose ontstaat. Na 20 tot 30 jaar heeft ongeveer 20 tot 30% van de personen met een chronische HCV-infectie lever cirrose ontwikkeld, littekenweefsel in de lever dat de leverfunctie aantast. Het hebben van levercirrose geeft een risico op het ontstaan van leverkanker (1 tot 5% per jaar bij een chronische HCV-infectie), bloedingen van slokdarmspataders, en leverfalen.

Naar schatting waren er in 2020 wereldwijd 58 miljoen personen met een chronische HCV-infectie. In Nederland komen HCV-infecties relatief gezien weinig voor. Volgens de meest recente schattingen waren er in Nederland in 2016 ongeveer 23,000 nog levende personen die ooit een chronische HCV-infectie hadden. HCV wordt overgedragen via bloed-bloedcontact. De meest voorkomende routes van HCV-overdracht zijn via besmette medische uitrusting, het toedienen van bloedproducten, en onsteriele naalden voor injecterend drugsgebruik of tatoeages. In Nederland komen de eerste twee routes van HCV-overdracht vrijwel niet meer voor sinds het begin van de jaren ’90. Naast deze routes komt HCV-overdracht voor tussen mannen die seks hebben met mannen, voornamelijk degenen die leven met humaan immunodeficiëntievirus (hiv) of die hiv pre-expositie profylaxe (PreP) gebruiken. Populaties waarbij HCV-infecties het meeste voorkomen zijn gerelateerd aan de bovengenoemde besmettingsroutes. De meeste HCV-infecties in Nederland komen voor bij migranten uit landen waar HCV veel voorkomt, voornamelijk Afrika, Oost-Europa en Azië. Andere populaties met een relatief hoge HCV-prevalentie zijn personen met een geschiedenis van injecterend drugsgebruik, mannen die seks hebben met mannen, en personen met aangeboren stollingsstoornissen zoals hemofilie.

Er bestaat geen werkend vaccin tegen HCV, maar er zijn wel antivirale medicijnen die worden gebruikt om HCV-infecties te genezen. Tot 2014 werden chronische HCV-infecties behandeld met een combinatie van twee antivirale middelen: injecties die het immuunsysteem stimuleren virussen op te ruimen (zogeheten PEG-interferon injecties) en een antiviraal middel in tabletvorm (ribavirine). Deze behandeling duurde zes tot twaalf maanden, had zware bijwerkingen en had een relatief beperkte slagingskans. In 2014 kwam een nieuw type medicatie beschikbaar, de zogeheten direct werkende antivirale middelen (direct-acting antivirals, DAA). Na een behandeling van acht tot

twaalf weken met DAA is >95% van de behandelde personen genezen van de HCV-infectie, met daarbij relatief weinig bijwerkingen.

Mede vanwege de introductie van deze zeer succesvolle medicatie heeft de Wereldgezondheidsorganisatie in 2016 het doel gesteld om HCV in 2030 te elimineren als een bedreiging voor de wereldwijde publieke gezondheid. Het doel van dit proefschrift was het beschrijven van resterende uitdagingen voor HCV-eliminatie in het tijdperk van direct werkende antivirale middelen en de benodigde stappen om HCV-eliminatie te bereiken. Het proefschrift bestaat uit drie delen, die zijn onderverdeeld in meerdere hoofdstukken. In de eerste twee delen wordt gefocust op HCV-eliminatie binnen twee specifieke doelgroepen, namelijk personen met hemofilie en personen die leven met hiv. In het derde deel worden algemene uitdagingen voor HCV-eliminatie in Nederland beschreven.

Belangrijkste bevindingen van dit proefschrift

- Nederland is op koers om in of vlak na 2030 te voldoen aan de door de Wereldgezondheidsorganisatie gestelde doelen voor hepatitis C-eliminatie. Om dit daadwerkelijk te bereiken is het cruciaal dat het aantal personen dat op HCV getest en voor HCV behandeld wordt niet te veel terugloopt.
- Voor de populaties van personen met hemofilie en personen die leven met hiv is HCV-eliminatie reeds binnen handbereik, mede dankzij het grote aantal personen dat is behandeld met DAA therapie na het beschikbaar komen hiervan.
- Het bewustzijn over, en de kennis van, potentieel resterende gevolgen van succesvol behandelde HCV-infectie moet worden vergroot bij behandelaren van personen met hemofilie. Dit betreft de noodzaak voor continueren van leverkankersurveillance bij personen met gevorderde fibrose of cirrose van de lever na HCV-genezing, en het evalueren van de behoefte aan psychosociale ondersteuning bij personen met hemofilie en een genezen HCV infectie.
- Doelgroep-specifieke HCV-eliminatiedoelen moeten worden geïmplementeerd voor micro-eliminatie doeleinden. Het terugbrengen van de prevalentie van HCV-viremie moet worden toegevoegd aan de eliminatiedoelen die momenteel worden gebruikt, met name voor personen met een verleden van injecterend drugsgebruik.
- Decentralisatie van HCV-behandeling, dat wil zeggen het aanbieden van HCV-behandeltrajecten buiten ziekenhuizen die gespecialiseerde HCV-behandelcentra zijn, moet mogelijk worden gemaakt en worden aangemoedigd om barrières voor HCV-behandeling te verlagen.
- Het her-opsporen van gediagnosticeerde maar uit zorg geraakte personen met een HCV-infectie kan bijdragen aan HCV-eliminatie door het verminderen van het aantal personen met een chronische HCV-infectie en door bij te dragen aan epidemiologische kennis. Herhaalde her-opsporingsinitiatieven moeten worden aangemoedigd. HCV her-opsporing draagt naar alle waarschijnlijkheid bij aan het verminderen van HCV-gerelateerde mortaliteit, gezien een aanzienlijk deel van de opgespoorde personen gevorderde fibrose of cirrose van de lever heeft.
- Het is onwaarschijnlijk dat een verminderde effectiviteit van DAA-behandeling HCV-eliminatie zal belemmeren voor personen met een zeldzaam HCV-genotype in Nederland, of uit Afrika of Azië afkomstige personen die leven met hiv in Europa. Desondanks is het belangrijk om de effectiviteit van DAA bij zeldzame HCV-genotypes wereldwijd te bevestigen en te monitoren.
- Personen met HCV-gerelateerde levercirrose moeten halfjaarlijkse surveillance van leverkanker worden aangeboden, onafhankelijk van succesvolle DAA-behandeling of verbeterde non-invasieve parameters van leverfibrose na HCV-genezing.

Samenvatting resultaten

Dit proefschrift bestaat uit drie delen, onderverdeeld in verschillende hoofdstukken. **Deel 1** focust zich op de populatie van personen met hemofilie. **Hoofdstuk 2** betreft een literatuurreview die de geschiedenis en huidige situatie van de virale hepatitis epidemie bij personen met hemofilie beschrijft. **Hoofdstuk 3** beschrijft een studie met gegevens over de lever-gerelateerde uitkomsten van langdurige HCV-infectie bij personen met hemofilie, met focus op de situatie na succesvolle behandeling van HCV. We vonden dat lever-gerelateerde complicaties, voornamelijk leverkanker, ook na genezing van HCV nog regelmatig voorkomen bij personen met gevorderde leverfibrose of cirrose. Deze resultaten wijzen erop dat leverkankersurveillance na HCV-genezing nodig blijft voor deze groep. In **hoofdstuk 4** bleek uit data van een landelijke studie dat personen met hemofilie en een succesvol behandelde HCV-infectie een lagere kwaliteit van leven hebben dan personen met hemofilie die nooit een chronische HCV-infectie hebben gehad.

In **deel 2** worden resterende uitdagingen voor HCV-eliminatie bij personen die leven met hiv beschreven. Uit de landelijke studie beschreven in **hoofdstuk 5** bleek dat sinds de introductie van DAA de prevalentie van HCV-viremie sterk is gedaald bij personen die leven met hiv in Nederland. Hiernaast werden verschillende factoren gevonden die waren geassocieerd met een lagere kans op het initiëren van DAA-behandeling, waaronder het behoren tot de populatie van personen met een verleden van injecterend drugsgebruik. **Hoofdstuk 6** beschrijft een grote internationale studie waarin gegevens van personen met hiv/HCV co-infectie uit negen cohorten uit zes verschillende hoge-inkomenslanden werden gebruikt. Uit deze studie bleek dat er tussen deze landen verschillen waren in de snelheid van het starten van DAA-behandeling na het beschikbaar komen van deze therapie. Hierbij bleek dat de snelheid van het starten van DAA-behandeling in Nederland hoger was dan het gemiddelde van deze hoge-inkomenslanden. **Hoofdstuk 7** beschrijft een studie waarin data van personen die leven met hiv van verschillende Europese cohorten werd gecombineerd. Hieruit bleek dat DAA-behandeling leidt tot een hoog percentage genezing bij personen met hiv/HCV uit Afrika en Azië, regio's waar HCV-genotypes geassocieerd met DAA-resistentie frequent voorkomen.

Deel 3 beschrijft uitdagingen voor het elimineren van HCV in Nederland in het algemeen. **Hoofdstuk 8** beschrijft de resultaten van een landelijk her-opsporingsproject, waarbij in totaal 219 eerder gediagnosticeerde maar uit zorg geraakte mensen met HCV succesvol terug in zorg werden gebracht. Van deze personen had 28% een gevorderde leverfibrose of cirrose. In **Hoofdstuk 9** wordt een landelijke studie beschreven waarin DAA-effectiviteit bij personen met een zeldzaam HCV-genotype werd onderzocht. In deze studie werd een hoog percentage genezing gevonden, wat in overeenkomst is met DAA-effectiviteit bij

veelvoorkomende HCV-genotypes. **Hoofdstuk 10** betreft een literatuurreview waarin het voorkomen van leverkanker en bloedingen van slokdarmspataders bij patiënten met HCV-gerelateerde cirrose en een genezen HCV-infectie wordt beschreven. In **hoofdstuk 11** worden de resultaten van een modelleringsstudie beschreven waarin de voortgang van HCV-eliminatie in Nederland werd onderzocht. De resultaten wezen erop dat Nederland op koers is om eliminatie van HCV te bereiken in of vlak na 2030, onder de voorwaarde dat HCV diagnose- en behandelaantallen niet te veel dalen.

Tot slot wordt in de algemene slotbeschouwing in **hoofdstuk 12** de huidige stand van zaken wat betreft HCV epidemiologie in Nederland, resterende uitdagingen voor HCV eliminatie, en beleidswijzigingen benodigd om HCV eliminatie in Nederland vooruit te helpen beschreven.

LIST OF PUBLICATIONS

Related to this thesis

C.J. Isfordink*, S.M. Brakenhoff*, M. van Dijk*, et al. Hepatitis C elimination in the Netherlands (CELINE): study protocol for nationwide retrieval of lost to follow-up patients with chronic hepatitis C. BMJ Open Gastroenterol. 2020 Apr 12;7(1):e000396.

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CURRICULUM VITAE

Cas Joos Isfordink was born in Rheden on the 18th of December 1993, and grew up in Culemborg. In 2011, he started medical school at the University Medical Centre Utrecht. During his masters degree, he completed the extracurricular Honours Program by conducting research at the department of Hepatopancreaticobiliary surgery. In 2018, he completed his medical degree and started a PhD project on hepatitis C elimination at the department of Gastroenterology and Hepatology and the Van Creveldkliniek, department of Benign Haematology in the University Medical Centre Utrecht and the department of Infectious Diseases at the Amsterdam University Medical Centres, location AMC. Since the end of the PhD trajectory in the summer of 2022, he has been working as a medical resident internal medicine in the Tergooi Medical Centre in Hilversum.