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Hepatitis C Infection in Dutch HIV-positive Patients in the Era of Direct-acting Antiviral Therapy

Hepatitis C infectie bij Nederlandse Hiv-positieve patiënten
in het tijdperk van 'direct-acting antiviral' therapie

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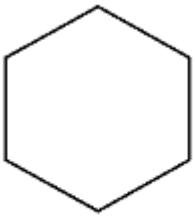


Chapter 1

General introduction and outline of the thesis

Hepatitis C infection

The hepatitis C virus and its discovery

The hepatitis C virus (HCV) is a small enveloped single-stranded RNA virus of positive polarity with liver tissue tropism. It belongs to the Hepacivirus genus and is a member of the Flaviviridae[1]. Until 1975, only two hepatitis viruses were known, but 65% of post-transfusion hepatitides were not caused by hepatitis A or B[2]. However, non-A non-B hepatitis was thought to be caused by an infectious agent as inoculation of a chimpanzee with serum of a patient with non-A non-B hepatitis was followed by a rise in liver enzymes [3,4] and this presumed infectious agent could be inactivated with chloroform[5]. Due to new cloning techniques for nucleic acid, in 1989 the genome of non-A non B hepatitis from an infected chimpanzee was characterized with cDNA, hence the name HCV[6].

Prevalence and genotype distribution world wide

It is estimated that globally 71 million people are living with HCV. Although HCV affects all global regions, major differences exist between and within countries. The most affected are the Eastern Mediterranean Region and European Region, with a prevalence of 2.3% and 1.5% respectively[7,8]. Of the hepatitis C genome from different regions, at least 7 different genotype are known (>30% difference between two nucleotide sequences). This may be further divided into at least 67 subtypes within these genotypes (20-25% difference between two nucleotide sequences)[9,10] and this number will probably rise as in the future even more samples will be sequenced.

Parenteral exposure as risk factor for hepatitis C transmission

Hepatitis C is a blood born virus which can be transmitted by parenteral exposure to blood and blood products[11,12], haemodialysis[13], non-sterile needles (nosocomial, intra-venous drug use, tattooing[14-16]) or infected transplant organs[17,18]. Due to screening of blood products the risk of acquiring hepatitis C through blood transfusion is now estimated to be as low as 1:500.000 to 1:1.000.000[19]. Transplant organizations now have strategies for HCV

screening. However, nosocomial HCV outbreaks in developed countries are still reported, for example through the re-use of contaminated syringes (despite using a new needle), the improper use of multidose vials used for multiple patients and in haemodialysis units[20]. Healthcare workers, especially those who come in close contact with infected patients and sharp objects, are at risk for HCV acquisition. However the incidence of seroconversion after exposure to an HCV positive source is estimated to be less than 2%[16] and a Dutch single-hospital cohort study showed that the prevalence among its healthcare workers (1/729; 0.14%) was not higher than that of the general population[21]. Another study showed that people with multiple tattoos and/or piercings in the Netherlands seem not to be at increased risk for HCV infections, as the authors did not find an increased seroprevalence in this risk group[22].

Intravenous drug use (IVDU) is one of the most important risk factors for parenteral HCV acquisition as was shown by the high prevalence of HCV in this population[23]. However, the development of opioid substitution therapy (OST) and needle syringe exchange programs (NSP) have been shown to firmly reduce the risk of HCV acquisition[24]. In the Netherlands most IVDU use took place during the sixties to the nineties and nowadays good OST and NSP have been implemented. However, in regions without proper preventive measures like OST and NSP, HCV transmission via IVDU remains an important health care problem[25].

Sexual transmission of hepatitis C

A large prospective cohort study showed that in serodiscordant (HCV discordant) monogamous heterosexual couples the long-term transmission risk was 0.001% or lower[26]. Interestingly, a relatively new subgroup of hepatitis C patients started to emerge last century. The first reports on sexually transmitted HCV infection in men who have sex with men (MSM) who denied IVDU started to merge in 2004 and 2005[27-29]. Sexual transmission of HCV in HIV-positive MSM will be described in more detail on pages 19 and 20.

Acute hepatitis C infection

Patients who become infected with hepatitis C virus can develop abnormal laboratory findings in the following order: detectable HCV RNA, then elevation in ALT, followed by HCV antibodies[30]. After inoculation there is a variable incubation period depending on transmission mode. High level viremia occurs usually within 1-2 weeks after inoculation in transfusion hepatitis cases, needle stick injuries or experimentally inoculated chimpanzees[31-33]. However, it is unknown if this can be extrapolated to low-inoculum infections. Fluctuation in HCV RNA levels has been reported as a hallmark of the viral dynamics in the early stages of HCV infection and some patients may even become temporarily HCV RNA negative[34-37]. There is a considerable heterogeneity among individuals, as some patients may show quite high HCV RNA levels, some patients may show spontaneous clearance beyond six months or have a large HCV RNA decline during acute HCV infection without spontaneous clearance[34]. Within 40-50 days after high level viremia, ALT levels will start to rise, showing that there is some degree of liver cell injury[31,38]. The elevation of aminotransferases varies greatly between individuals. High ALT levels seem to be correlated with seroconversion[31,38], however, in some patients, especially in HIV-coinfected patients, seroconversion can be delayed. In a series with 43 HIV-positive patients with acute HCV infection, after three months 37% of patients still had a negative antibody test. After 9 months, 10% of patients still had a negative antibody test[39]. In fact, some patients stay undetectable for antibodies for years[40].

Acute hepatitis is most often asymptomatic, most patients do not develop icterus and fulminant hepatitis is rare. A study that was designed to include symptomatic patients infected with HCV, reported non-specific symptoms like jaundice, influenza like symptoms, dark urine, discoloured stools, nausea and discomfort in the right upper quadrant of the abdomen[41]. However, due to the subclinical course of HCV infection, and the fact that symptoms of an acute HCV infection are non-specific, it is important to screen high risk groups. Case definitions for acute hepatitis C virus infection vary considerably between studies[42].

There is a lack of evidence on when 'acute' infection becomes 'chronic' especially since the precise timing of infection is usually problematic. Acute HCV is often defined as the somewhat arbitrarily chosen period of the initial 6 months following exposure, in other words, the phase of the infection with fluctuating ALT and HCV RNA and the time window in which spontaneous viral clearance can occur[34]. However, this phase may last much longer in some patients [43] and a large multinational acute HCV cohort study showed that 34%, 67%, and 83% of patients demonstrated clearance at resp. 3, 6, and 12 months[44]. A consensus definition was created by the European AIDS Treatment Network (NEAT) acute hepatitis C infection consensus panel in 2011 and is shown in table 1[45].

Table 1 Consensus definitions acute hepatitis C infection NEAT [45]

Preferred criteria
(1) Positive anti-HCV immunoglobulin G (IgG) in the presence or absence of a positive HCV-RNA and a documented negative anti-HCV IgG in the previous 12 months. (2) Positive HCV-RNA and a documented negative HCV-RNA and negative anti-HCV IgG in the previous 12 months.
Alternative criteria *if tests in the past year are lacking*
Positive HCV-RNA regardless of anti-HCV IgG with any of the following two conditions: (a) An acute rise in ALT greater than 10 times the ULN. (b) An acute rise in ALT greater than five times the ULN, with documented normal ALT within 12 months.

Chronic hepatitis C

The hallmark of HCV is its ability to establish persistent (chronic) infection, which occurs in approximately 75% of cases[46]. Persistence of HCV is probably multifactorial and arises from the combination of an inadequate human immune response in combination with the immune evasive character of the HCV virus itself[47,48]. In cohort studies, spontaneous clearance of hepatitis C seemed to be associated with female gender, younger age, symptomatic acute HCV infection, interleukine-28 B CC genotype, HCV genotype 1 and a high peak HCV RNA level[44,46,49,50]. For HIV-coinfected patients, several studies have shown that the rate of spontaneous clearance is significantly lower — in the range of 10 to 20%[49,51]. If a patient does not spontaneously clear the virus, chronic hepatitis C infection will develop. In chronically infected patients, persistent hepatic inflammation can lead to cirrhosis in 10-20% of patients over 20-30 years. Once cirrhosis has developed there is a 1–5% annual risk of HCC and a 3–6% annual risk of hepatic decompensation[52,53].

Treatment of hepatitis C with direct-acting antivirals

Since the discovery of HCV, there has been a revolution in hepatitis C treatment options and efficacy of HCV therapy. Sustained virological response has improved from 2-7% for interferon monotherapy from the 90ties onwards to as high as 98% for the second generation DAA combination therapies. This revolution coincides with the unravelling of the structure and function of hepatitis C and its proteins which led to the development of the direct-acting antivirals[54]. However, most HCV clinical trials are single arm studies without randomization, almost no head to head trials have been executed and study populations are difficult to compare due to different ethnical and socioeconomic backgrounds and different routes of HCV transmission. The proteins involved in HCV polyprotein processing, HCV RNA replication and virion assembly are a target for therapy and will be discussed in this paragraph.

Structural and functional analysis of the hepatitis C virus

For a long time, the analysis of hepatitis C was difficult as serum-derived virus is not easily ultra-filtered because of its association with low-density lipoproteins[55-57]. Furthermore, a cell culture for hepatitis C replication did not exist. It has taken a decade after the discovery of its genome in 1989 before the first research on non-infectious hepatitis C virus replication in the human hepatoma cell line Huh7 was possible[58]. Another 15 years were needed to visualize cell free virions with cryo-electron and negative-stain transmission electron microscopy[59,60] and to develop an efficient infectious cell culture system which allowed functional assays for treatment targets[59]. Viruses isolated from cell cultures have a spherical shape with a diameter around 50-55 nm. Using 3D modelling of the HCV-like particles and genomic comparison with other Flavivirusses, it was assumed that 90 copies of a block of two heterodimers of HCV proteins E1 and E2 forms the outer layer of the virions with an diameter of approximately 50 nm. Two viral glycoproteins, E1 and E2, are embedded in the lipid envelope. This outer layer surrounds a lipid bilayer that contains the viral nucleocapsid consisting of the HCV core protein that contains the genomic viral RNA[60]. The HCV genome has a length of approximately 9.6 kb. The single strand RNA genome of

this virus is 9100 nucleotides long, a single open reading frame that encodes for 10 proteins, 3 structural proteins and 7 non-structural proteins of which NS3/4A, NS5A and NS5B are targeted today with direct-acting antiviral therapy[54].

The hepatitis C NS3/4A proteins

The N-terminus of the NS3 protein has serine protease activity and requires interaction with NS4A to cleave the rest of the downstream polyprotein[61]. The HCV NS3/4A protein also cleaves MAVS which blocks RIG-I signalling and prevents IFN induction in response to viral infection[62]. Both functions make NS3/4A an attractive target for inhibition therapy. The location of the active side of NS3/4A protease (a shallow groove) made de design of compound inhibitors quite difficult[63], but today both macrocyclic and linear tetra-peptide-based α-ketoamide derivates have been developed which inhibit the NS3/4A protein.

The hepatitis C NS5A protein

The NS5A protein has multiple functions in HCV replication, viral assembly and virion release. Although the action of NS5A inhibitors is not based on blocking enzymatic activity and the exact mechanism of action is still not clear[64], NS5A inhibitors were shown to be highly potent.

The hepatitis C NS5B protein

The NS5B protein is an RNA-dependent RNA-polymerase[65]. It is positioned in the ER membrane with the active sides of the polymerase located in the cytoplasm. It is an important compound of the HCV replication complex situated in the NS4B-induced membranous web[66]. The cytosolic part of this viral enzyme forms a right-handed connected structure with a palm, fingers and a thumb[65]. Nucleoside analogue polymerase inhibitors (like sofosbuvir) are built into the RNA chain causing chain termination[67]. As the active side of the NS5B protein is highly conserved, nucleoside inhibitors are potentially pan-genotypic and have a high barrier to resistance. Non-nucleoside analogue polymerase inhibitors (like dasabuvir) bind to allosteric enzyme sites which results in conformational protein change[68].

Direct-acting antiviral therapy

Direct-acting antiviral therapy should be prescribed according to the genotype of the patient as most but not all currently used regimens are pan-genotypic[69]. Furthermore, different classes of DAA's should always be combined as resistance will appear promptly under most DAA monotherapies[70]. Due to the extremely high replication rate of HCV and the error prone polymerase enzyme which lacks proofreading, many quasispecies (HCV variants) arise within one patient soon after infection[71] harbouring resistance associated variants (RAS). Both, naturally occurring polymorphisms [72], and drug-induced RAS can be detected. Drug-induced RAS with a relative higher fitness compared to wild-type virus can emerge during treatment and result in treatment failure[73].

In the case of therapy failure and the emergence of drug-induced RAS, some types of these RAS can revert back to wild type, while others do not or to a lesser extent. In general, NS5A RAS persist longer than NS3 RAS, as NS5A RAS can stay detectable >96 weeks after treatment[74-76]. Most direct-acting antivirals are only available as co-formulations and combining individual compounds often is much more expensive. In the fall of 2017, the termination of the further clinical development of two new DAA's was announced[77,78]. This may mark the end of an unprecedented era of DAA development.
Currently approved and recommended DAA's for the treatment of chronic HCV in the Europe and the Netherlands are: NS3 protease inhibitors: paritaprevir, grazoprevir, voxilaprevir and glecaprevir; NS5A inhibitors: ledipasvir, ombitasvir, daclatasvir, elbasvir, velpatasvir and pibrentasvir; NS5B polymerase inhibitors: sofosbuvir and dasabuvir[69,79-81].

Sofosbuvir (Solvaldi®) and daclatasvir (Daklinza®) are available as individual compounds, the other DAA's are only available as combination tablets:

- sofosbuvir/ledipasvir 1 tablet once daily (Harvoni®) registered for genotypes 1, 3, 6;
- grazoprevir/elbasvir 1 table once daily (Zepatier®) registered for genotypes 1, 4;
- sofosbuvir/velpatasvir 1 tablet once daily (Epclusa®) registered for genotypes 1-6;
- glecaprevir/pibrentasvir 3 tablets once daily (Maviret®) registered for genotypes 1-6;
- sofosbuvir/ledipasvir/voxilaprevir 1 tablet once daily (Vosevi®)[80,81] registered for 1-6.

Hepatitis C elimination

Due to the rapidly evolving field, we have made hepatitis C a curable disease for almost all patients in a time span of 30 years, from its discovery in 1989 until today[54]. However, if an infectious disease is curable, this does not automatically mean that it is possible to eradicate, eliminate or even control this disease. It is important to distinguish these three definitions. 'Eradication' is defined as permanent reduction to zero of the worldwide incidence, 'elimination' as reduction to zero of the incidence of infection caused by a specific agent in a defined geographical area and 'control' as the reduction of disease incidence, prevalence, morbidity or mortality to a locally acceptable level[82].

In 2016 the World Health organization released a global health sector strategy on viral hepatitis which is part of the 2030 Agenda for Sustainable Development. One of these goals is striving towards the elimination of HCV as a public health threat, and this is defined as a 90% reduction in new HCV infections (incidence) and a 65% reduction of HCV-related deaths (mortality) by 2030. Priority actions in the plan to reach these hepatitis C elimination impact targets are :

- development of an information system to understand the hepatitis C epidemic and focus the response on the countries specific epidemic;
- define high-impact interventions on the continuum of care and hepatitis C services;
- strengthen the delivery of these services to achieve maximum impact and equality;
- propose strategies to reduce costs;
- and promote innovation to drive rapid progress[83].

Barriers for hepatitis C elimination are that only few countries have national hepatitis plans embracing the points described above, national data on epidemics can be lacking and (key) populations are hidden or marginalized, thereby increasing vulnerability and preventing equal access to services. The continuum of hepatitis C care should be tailored to the specific epidemic within a country to curb the epidemic in order to reach the elimination goals. Furthermore, effective interventions should be combined and tailored for the specific population, location and setting. In the next paragraph the hepatitis C epidemic in the Netherlands in general and, more specific, in Dutch HIV-positive MSM will be described.

Hepatitis C in the Netherlands

Who are at risk for hepatitis C in the Netherlands

The exact total prevalence of HCV in the Netherlands is not known. This may be explained by the fact that data were derived from measuring either HCV RNA in blood or anti-HCV antibodies in a random sample of the Dutch population or measuring anti-HCV antibody prevalence in specific risk groups. From 1995 to 2014, 220 HCV RNA positive samples were found in a cohort of 868,095 new (first time) unpaid blood donors (prevalence 0.03%). The highest prevalence was found in 1999 and gradually declined thereafter. However, this number is probably an underestimation as in the Netherlands persons with (self-reported) risk behaviour for HIV infections are actively excluded from blood donation[84]. In the PIENTER-2 study, cross-sectional serum samples were collected from the Dutch population via municipal registers between 2006-2007. In this study, a large sample of most prevalent migrant groups in the Netherlands was included (as they were underrepresented in earlier studies). In total, 14 out of 4446 samples were anti-HCV positive (0.30%; 95% C.I. 0.05-0.55%), with a prevalence of 0.17% (95% C.I. 0.00-0.36%) for indigenous Dutch inhabitants and 2.12% (95% C.I. 0.46-3.78%) for first generation migrants from endemic countries.

However, the number of HIV-positive MSM and persons reporting IVDU were small in this study[85]. In 2013, Vriend et al. reported on the combined outcomes of Dutch prevalence studies for HCV in the general population as well as in specific risk groups (migrants, MSM and people who inject drugs) to estimate the Dutch HCV prevalence. The estimated national seroprevalence of HCV was 0.22% (min 0.07%, max 0.37%)[86]. Besides these cross-sectional data, other studies gave more insight into the longitudinal incidence of hepatitis C infections in IVDU en HIV-positive MSM in the Netherlands during the last two decades. In a retrospective cohort study from Amsterdam that ran from 1985 to 2005, the HCV incidence dropped significantly among IVDU[23]. Meanwhile, the incidence of HCV in HIV-positive MSM increased (which will be discussed at page 20)[87-90].

Screening for hepatitis C in the Netherlands

On the first of November 2016, the health counsel of the Netherlands released a report on the screening of hepatitis C[91]. They advised against a nationwide screening of all Dutch inhabitants, due to the low overall HCV prevalence in the Netherlands. Instead they advised case finding, by screening for HCV in specific risk groups, such as first-generation migrants/refugees from endemic countries (with endemic being defined as ≥2% HCV prevalence), (former) people who inject drugs (most IVDU use dates from 1960-1990) whom due to longstanding NSP and OST are most probably already reintegrated in society, MSM ('testing the HIV-positive and at least monitor the HIV-negative'[92,93]). Furthermore, they advised retracing of patients who were previously diagnosed with HCV infection but got lost to follow up before curation of HCV. Because of lack of studies on the efficiency of screening in the Dutch setting, there are no cost-effectiveness analysis on screening (and sub sequential treatment) for HCV for these different risk groups.

Regarding MSM, further recommendations on screening can be found in the following guidelines. The Dutch National HIV Guideline from the 'Nederlandse Vereniging voor HIV Behandelaren' advises to screen all new HIV patients for HCV with HCV antibodies upon entry into HIV care and screen sexually active HIV-positive MSM annually with HCV antibodies[94]. Furthermore, the Dutch National Institute for Public Health and the Environment's (RIVM) guideline on sexual health for STI clinics advises screening for hepatitis C with HCV antibodies in HIV positive MSM, MSM notified for being exposed to HCV and MSM diagnosed with a lymphogranuloma venereum infection regardless of HIV status and MSM refusing an HIV test[95].

The hepatitis C epidemic in Dutch HIV-positive men who have sex with men

For the remaining part of this thesis, we will primarily focus on the hepatitis C epidemic in HIV-positive MSM. In 2004 and 2005 the first publications on possible sexual transmission of HCV in HIV-positive MSM appeared as hepatitis C unexpectedly started to emerge as a sexually transmitted disease in this population[27-29,96]. Evolutionary analysis of MSM-specific HCV strains showed that HCV had possibly been introduced into the MSM network before

1996-2000, but the vast expansion started only after the nineties, coinciding with the widespread introduction of HAART[97-99]. Epidemics in HIV-positive MSM were seen globally in high income countries, such as Europe, the USA, Canada, Australia, Taiwan and China[100,101]. For most low income countries data on the prevalence of HCV in HIV positive MSM are scarce, but the prevalence of an actively replicating HCV infection in HIV-infected patients in Africa seems to be much lower than estimated before[7,102]. However, since HIV-positive MSM are often not recognized as a key population in low income countries, data are lacking for this specific high risk population.

For the Netherlands, cohort studies among HIV-positive MSM in Amsterdam showed that the HCV incidence in this population rose from 1995 onwards, with a peak around 2005-2008 and a stabilizing high incidence around 12/1000 PYFU afterwards[87-89]. However, the epidemic in Dutch HIV-positive MSM was not limited to the Dutch capital as HCV infections were reported from all over the Netherlands[103,104]. Moreover, phylogenetic studies have shown that local outbreaks in Europe were part of a European transmission network of MSM-specific HCV lineages with mainly genotype 1a and 4 infections, which did not overlap with strains circulating in IVDU networks[99]. In contrast, acute HCV infections in HIV-positive MSM in the USA and Australia showed limited overlap with the European network and in Australia mainly genotype 1a and 3a were showing an overlap with IVDU networks[99,105,106].

The specific pathophysiological reason why HCV emerged as a sexually transmitted infection in this key population is not exactly clear. Hepatitis C is secreted in sperm[107] and risk factors for permucosal transmission of the virus like (traumatic) sexual practices and ulcerating sexually transmitted infections seem to be independently associated with acute HCV infection. In one of the first case-control studies into sexual risk behaviour for HCV infection, cases reported more sexual partners, more group sex, more receptive and insertive unprotected anal intercourse, a higher percentage of use of toys and fisting and cases were more likely to have shared drugs via a nasal or anal route [108]. In two more recent case-control studies in the Netherlands and Belgium, receptive unprotected anal intercourse, douching before anal intercourse, sharing sex toys, unprotected fisting, injecting drugs, sharing straws when snorting drugs and a documented gonorrhoea or

chlamydial infection in the 6-12 months before study entry, were independently associated with HCV acquisition[109,110].

In this thesis, we will look at the current HCV epidemic among HIV-positive MSM in the Netherlands and discuss different strategies to reduce the transmission of HCV within this population. We will specifically use this epidemic to investigate and discuss the possibility of micro-elimination within this key population as the Dutch HIV positive MSM population is well-defined and regularly screened for HCV infection.

Aims and outline of this thesis

The overall aim of the research described in this thesis is to investigate and discuss possible strategies and barriers for micro-elimination of HCV among Dutch HIV-positive MSM in the era of DAA.

In **part A** of this thesis focuses on the effectivity of two interventions which could contribute to combating hepatitis C towards its elimination as a public health threat: the shortening of direct-acting antiviral therapy for chronic hepatitis C infection as well as for acute hepatitis C infection. Shortening of therapy can lead to an improved compliance and a reduction of costs which is one of the WHO's priority actions to reach the hepatitis C elimination targets. Moreover, if DAA's are effective during the acute phase of hepatitis C infection, treating high risk patients during the acute phase of infection can reduce (sexual) transmission of HCV to others, thereby reducing the HCV incidence in this key population.

In **Chapter 2**, the effectivity of 8 weeks of ledipasvir/sofosbuvir for *chronic* genotype 4 hepatitis C infected direct-acting antiviral-naive HIV-positive and -negative patients without cirrhosis is evaluated. **Chapter 3** investigates whether grazoprevir/elbasvir is effective when given during the *acute* phase of HCV and whether treatment duration can be shortened during the acute phase of an HCV infection without loss of effectiveness.

Part B of this thesis focuses on the effects of two recent developments on the hepatitis C epidemic among Dutch HIV-positive MSM, as they are a well-defined key population and frequently monitored for hepatitis C infection. Besides the strategies which could contribute hepatitis C elimination among Dutch HIV-positive MSM as described in part A, in this part we also discuss the effects of: the recent unrestricted availability of direct-acting antivirals for chronic HCV infection and the introduction of HIV pre-exposure prophylaxis.

In Chapter 4, the treatment uptake and treatment success of direct-acting antiviral hepatitis C therapy in HIV-positive patients in the Netherlands is investigated. Chapter 5 focuses on the acute hepatitis C incidence before and after the unrestricted availability of direct-acting antiviral for chronic hepatitis C among Dutch HIV-positive MSM.

Chapter 6 describes the acute hepatitis C infections among HIV-negative MSM who exhibit sexual high risk behaviour and/or use HIV pre-exposure prophylaxis.

Finally, in part C of this thesis the possibility of micro-elimination of HCV among Dutch HIV-positive MSM in the era of direct-acting antivirals is discussed. In Chapter 7 the possibility of hepatitis C elimination among people living with HIV is discussed. Finally, Chapter 8 summarizes the results of this thesis and future perspectives for HCV elimination of HCV among Dutch HIV-positive MSM in the era of DAA's are discussed.

References

1. Stapleton JT, Foung S, Muerhoff AS, Bukh J, Simmonds P. The GB viruses: a review and proposed classification of GBV-A, GBV-C (HGV), and GBV-D in genus Pegivirus within the family Flaviviridae. J Gen Virol 2011;92:233-46.
2. Feinstone SM, Kapikian AZ, Purcell RH, Alter HJ, Holland PV. Transfusion-associated hepatitis not due to viral hepatitis type A or B. N Engl J Med 1975;292:767-70.
3. Alter HJ, Purcell RH, Holland PV, Popper H. Transmissible agent in non-A, non-B hepatitis. Lancet 1978;1:459-63.
4. Hollinger FB, Gitnick GL, Aach RD, et al. Non-A, non-B hepatitis transmission in chimpanzees: a project of the transfusion-transmitted viruses study group. Intervirology 1978;10:60-8.
5. Feinstone SM, Mihalik KB, Kamimura T, Alter HJ, London WT, Purcell RH. Inactivation of hepatitis B virus and non-A, non-B hepatitis by chloroform. Infect Immun 1983;41:816-21.
6. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989;244:359-62.
7. WHO. Global hepatitis report 2017. Accessed at 26-06-2018.
8. Leblebicioglu H, Arends JE, Ozaras R, et al. Availability of hepatitis C diagnostics and therapeutics in European and Eurasia countries. Antiviral Res 2018;150:9-14.
9. Smith DB, Bukh J, Kuiken C, et al. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource. Hepatology 2014;59:318-27.
10. Simmonds P, Bukh J, Combet C, et al. Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes. Hepatology 2005;42:962-73.
11. Alter HJ, Purcell RH, Shih JW, et al. Detection of antibody to hepatitis C virus in prospectively followed transfusion recipients with acute and chronic non-A, non-B hepatitis. N Engl J Med 1989;321:1494-500.
12. Francois M, Dubois F, Brand D, et al. Prevalence and significance of hepatitis C virus (HCV) viremia in HCV antibody-positive subjects from various populations. J Clin Microbiol 1993;31:1189-93.
13. Fissell RB, Bragg-Gresham JL, Woods JD, et al. Patterns of hepatitis C prevalence and seroconversion in hemodialysis units from three continents: the DOPPS. Kidney Int 2004;65:2335-42.
14. Sutton AJ, Hope VD, Mathei C, et al. A comparison between the force of infection estimates for blood-borne viruses in injecting drug user populations across the European Union: a modelling study. J Viral Hepat 2008;15:809-16.
15. Haley RW, Fischer RP. Commercial tattooing as a potentially important source of hepatitis C infection. Clinical epidemiology of 626 consecutive patients unaware of their hepatitis C serologic status. Medicine (Baltimore) 2001;80:134-51.
16. Service USPH. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. MMWR Recomm Rep 2001;50:1-52.
17. Pereira BJ, Milford EL, Kirkman RL, Levey AS. Transmission of hepatitis C virus by organ transplantation. N Engl J Med 1991;325:454-60.
18. Roth D, Zucker K, Cirocco R, et al. The impact of hepatitis C virus infection on renal allograft recipients. Kidney Int 1994;45:238-44.
19. Pomper GJ, Wu Y, Snyder EL. Risks of transfusion-transmitted infections: 2003. Curr Opin Hematol 2003;10:412-8.
20. Pozzetto B, Memmi M, Garraud O, Roblin X, Berthelot P. Health care-associated hepatitis C virus infection. World J Gastroenterol 2014;20:17265-78.
21. Zaaijer HL, Appelman P, Frijstein G. Hepatitis C virus infection among transmission-prone medical personnel. Eur J Clin Microbiol Infect Dis 2012;31:1473-7.
22. Urbanus AT, van den Hoek A, Boonstra A, et al. People with multiple tattoos and/or piercings are not at increased risk for HBV or HCV in The Netherlands. PLoS One 2011;6:e24736.

23. van den Berg CH, Smit C, Bakker M, et al. Major decline of hepatitis C virus incidence rate over two decades in a cohort of drug users. Eur J Epidemiol 2007;22:183-93.
24. Platt L, Minozzi S, Reed J, et al. Needle syringe programmes and opioid substitution therapy for preventing hepatitis C transmission in people who inject drugs. Cochrane Database Syst Rev 2017;9:CD012021.
25. Hodder S. The opioid epidemic and infectious diseases: A public health crisis. Conference on Retroviruses and Opportunistic Infections (CROI), March 4–7, 2018 Boston, Abstract number 163.
26. Vandelli C, Renzo F, Romano L, et al. Lack of evidence of sexual transmission of hepatitis C among monogamous couples: results of a 10-year prospective follow-up study. Am J Gastroenterol 2004;99:855-9.
27. Browne R, Asboe D, Gilleece Y, et al. Increased numbers of acute hepatitis C infections in HIV positive homosexual men; is sexual transmission feeding the increase? Sex Transm Infect 2004;80:326-7.
28. Gotz HM, van Doornum G, Niesters HG, den Hollander JG, Thio HB, de Zwart O. A cluster of acute hepatitis C virus infection among men who have sex with men--results from contact tracing and public health implications. Aids 2005;19:969-74.
29. Gambotti L, Batisse D, Colin-de-Verdiere N, et al. Acute hepatitis C infection in HIV positive men who have sex with men in Paris, France, 2001-2004. Euro Surveill 2005;10:115-7.
30. Maheshwari A, Ray S, Thuluvath PJ. Acute hepatitis C. Lancet 2008;372:321-32.
31. Busch MP. Insights into the epidemiology, natural history and pathogenesis of hepatitis C virus infection from studies of infected donors and blood product recipients. Transfus Clin Biol 2001;8:200-6.
32. Thimme R, Oldach D, Chang KM, Steiger C, Ray SC, Chisari FV. Determinants of viral clearance and persistence during acute hepatitis C virus infection. J Exp Med 2001;194:1395-406.
33. Prince AM, Pawlotsky JM, Soulier A, et al. Hepatitis C virus replication kinetics in chimpanzees with self-limited and chronic infections. J Viral Hepat 2004;11:236-42.
34. Hajarizadeh B, Grebely J, Applegate T, et al. Dynamics of HCV RNA levels during acute hepatitis C virus infection. J Med Virol 2014;86:1722-9.
35. Smith JA, Aberle JH, Fleming VM, et al. Dynamic coinfection with multiple viral subtypes in acute hepatitis C. J Infect Dis 2010;202:1770-9.
36. Loomba R, Rivera MM, McBurney R, et al. The natural history of acute hepatitis C: clinical presentation, laboratory findings and treatment outcomes. Aliment Pharmacol Ther 2011;33:559-65.
37. Thomson EC, Fleming VM, Main J, et al. Predicting spontaneous clearance of acute hepatitis C virus in a large cohort of HIV-1-infected men. Gut 2011;60:837-45.
38. Glynn SA, Wright DJ, Kleinman SH, et al. Dynamics of viremia in early hepatitis C virus infection. Transfusion 2005;45:994-1002.
39. Thomson EC, Nastouli E, Main J, et al. Delayed anti-HCV antibody response in HIV-positive men acutely infected with HCV. Aids 2009;23:89-93.
40. Vanhommerig JW, Schinkel J, van der Valk M. Seven years of chronic hepatitis C virus infection in an HIV-infected man without detectable antibodies. Aids 2015;29:389-90.
41. Gerlach JT, Diepolder HM, Zachoval R, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. Gastroenterology 2003;125:80-8.
42. Hajarizadeh B, Grebely J, Dore GJ. Case definitions for acute hepatitis C virus infection: a systematic review. J Hepatol 2012;57:1349-60.
43. Orland JR, Wright TL, Cooper S. Acute hepatitis C. Hepatology 2001;33:321-7.
44. Grebely J, Page K, Sacks-Davis R, et al. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. Hepatology 2014;59:109-20.
45. Rockstroh J. Acute hepatitis C in HIV-infected individuals–recommendations from the NEAT consensus conference. AIDS 2011;25:399-409.
46. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat 2006;13:34-41.
47. Rehermann B. Hepatitis C virus versus innate and adaptive immune responses: a tale of coevolution and coexistence. J Clin Invest 2009;119:1745-54.

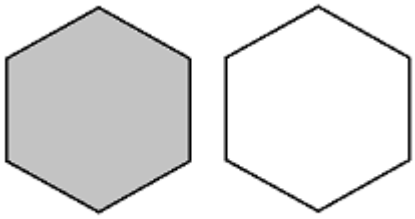
48. Bassett SE, Thomas DL, Brasky KM, Lanford RE. Viral persistence, antibody to E1 and E2, and hypervariable region 1 sequence stability in hepatitis C virus-inoculated chimpanzees. J Virol 1999;73:1118-26.
49. Smith DJ, Jordan AE, Frank M, Hagan H. Spontaneous viral clearance of hepatitis C virus (HCV) infection among people who inject drugs (PWID) and HIV-positive men who have sex with men (HIV+ MSM): a systematic review and meta-analysis. BMC Infect Dis 2016;16:471.
50. Martinello M, Matthews GV. Management of acute HCV in the era of direct-acting antivirals: implications for elimination. Lancet Gastroenterol Hepatol 2019.
51. Newsum AM, Schinkel J, van de Laar TJW, van der Meer JTM, Prins M. Spontaneous Clearance of Hepatitis C Virus Infection Among Human Immunodeficiency Virus-Infected Men Who Have Sex With Men. Open Forum Infect Dis 2017;4:ofx090.
52. Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol 2014;61:S58-68.
53. Seeff LB. Natural history of chronic hepatitis C. Hepatology 2002;36:S35-46.
54. Scheel TK, Rice CM. Understanding the hepatitis C virus life cycle paves the way for highly effective therapies. Nat Med 2013;19:837-49.
55. Thomssen R, Bonk S, Thiele A. Density heterogeneities of hepatitis C virus in human sera due to the binding of beta-lipoproteins and immunoglobulins. Med Microbiol Immunol 1993;182:329-34.
56. Agnello V, Abel G, Elfahal M, Knight GB, Zhang QX. Hepatitis C virus and other flaviviridae viruses enter cells via low density lipoprotein receptor. Proc Natl Acad Sci U S A 1999;96:12766-71.
57. Andre P, Komurian-Pradel F, Deforges S, et al. Characterization of low- and very-low-density hepatitis C virus RNA-containing particles. J Virol 2002;76:6919-28.
58. Lohmann V, Korner F, Koch J, Herian U, Theilmann L, Bartenschlager R. Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. Science 1999;285:110-3.
59. Wakita T, Pietschmann T, Kato T, et al. Production of infectious hepatitis C virus in tissue culture from a cloned viral genome. Nat Med 2005;11:791-6.
60. Yu X, Qiao M, Atanasov I, et al. Cryo-electron microscopy and three-dimensional reconstructions of hepatitis C virus particles. Virology 2007;367:126-34.
61. Love RA, Parge HE, Wickersham JA, et al. The conformation of hepatitis C virus NS3 proteinase with and without NS4A: a structural basis for the activation of the enzyme by its cofactor. Clin Diagn Virol 1998;10:151-6.
62. Saito T, Owen DM, Jiang F, Marcotrigiano J, Gale M, Jr. Innate immunity induced by composition-dependent RIG-I recognition of hepatitis C virus RNA. Nature 2008;454:523-7.
63. Bartenschlager R. The NS3/4A proteinase of the hepatitis C virus: unravelling structure and function of an unusual enzyme and a prime target for antiviral therapy. J Viral Hepat 1999;6:165-81.
64. Tellinghuisen TL, Marcotrigiano J, Rice CM. Structure of the zinc-binding domain of an essential component of the hepatitis C virus replicase. Nature 2005;435:374-9.
65. Lesburg CA, Cable MB, Ferrari E, Hong Z, Mannarino AF, Weber PC. Crystal structure of the RNA-dependent RNA polymerase from hepatitis C virus reveals a fully encircled active site. Nat Struct Biol 1999;6:937-43.
66. Romero-Brey I, Merz A, Chiramel A, et al. Three-dimensional architecture and biogenesis of membrane structures associated with hepatitis C virus replication. PLoS Pathog 2012;8:e1003056.
67. Koch U, Attenni B, Malancona S, et al. 2-(2-Thienyl)-5,6-dihydroxy-4-carboxypyrimidines as inhibitors of the hepatitis C virus NS5B polymerase: discovery, SAR, modeling, and mutagenesis. J Med Chem 2006;49:1693-705.
68. Beaulieu PL. Non-nucleoside inhibitors of the HCV NS5B polymerase: progress in the discovery and development of novel agents for the treatment of HCV infections. Curr Opin Investig Drugs 2007;8:614-34.
69. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. Journal of hepatology in press.
70. Sarrazin C, Kieffer TL, Bartels D, et al. Dynamic hepatitis C virus genotypic and phenotypic changes in patients treated with the protease inhibitor telaprevir. Gastroenterology 2007;132:1767-77.
71. Martell M, Esteban JI, Quer J, et al. Hepatitis C virus (HCV) circulates as a population of different but closely related genomes: quasispecies nature of HCV genome distribution. J Virol 1992;66:3225-9.

72. Newsum AM, Ho CK, Lieveld FI, et al. The hepatitis C virus nonstructural protein 3 Q80K polymorphism is frequently detected and transmitted among HIV-infected MSM in the Netherlands. Aids 2017;31:105-12.
73. Dietz J, Susser S, Vermehren J, et al. Patterns of Resistance-Associated Substitutions in Patients With Chronic HCV Infection Following Treatment With Direct-Acting Antivirals. Gastroenterology 2018;154:976-88 e4.
74. Wyles D, Mangia A, Cheng W, et al. Long-term persistence of HCV NS5A resistance-associated substitutions after treatment with the HCV NS5A inhibitor, ledipasvir, without sofosbuvir. Antivir Ther 2017.
75. Yoshimi S, Imamura M, Murakami E, et al. Long term persistence of NS5A inhibitor-resistant hepatitis C virus in patients who failed daclatasvir and asunaprevir therapy. J Med Virol 2015;87:1913-20.
76. P. Krishnan GS, T. Reisch, J. Beyer, T. Dekhtyar, M. Irvin, W. Xie, L. Larsen, T. Podsadecki, T. Pilot-Matias, C. Collins. Long-term follow-up of treatment-emergent resistance-associated variants in NS3, NS5A and NS5B with paritaprevir/r-, ombitasvir- and dasabuvir-based regimens. Journal of Hepatology, Volume 62, Supplement 2, Page S220, Volume 62, O057 2015.
77. Merck Discontinues MK-3682B and MK-3682C Development Programs. http://wwwmrknewsroomcom/ accessed at 29-06-2018 September 29, 2017.
78. Janssen to Discontinue Hepatitis C Development Program. https://wwwjnjcom/latest-news Accessed at 29-06-2018 September 11, 2017.
79. European public assessment reports (EPAR) published by the European Medicines Agency (EMA). wwwemaeuropaeu accessed at 29-06-2018.
80. Mauss B, Rockstroh, Sarrazin, Wedemeyer Hepatology – A clinical textbook. 2018;Ninth Edition.
81. HCV richtsnoer, update juli 2018. http://wwwhcvrichtsnoernl/;Accessed at 12-02-2019.
82. Dowdle WR. The principles of disease elimination and eradication. Bull World Health Organ 1998;76 Suppl 2:22-5.
83. WHO. Global health sector strategy on viral hepatitis 2016-2021, towards ending viral hepatitis. June 2016.
84. Slot E, Janssen MP, Marijt-van der Kreek T, Zaaijer HL, van de Laar TJ. Two decades of risk factors and transfusion-transmissible infections in Dutch blood donors. Transfusion 2016;56:203-14.
85. Vriend HJ, Op de Coul EL, van de Laar TJ, Urbanus AT, van der Klis FR, Boot HJ. Hepatitis C virus seroprevalence in the Netherlands. Eur J Public Health 2012;22:819-21.
86. Vriend HJ VVM, Prins M, Urbanus AT, Boot HJ, Op De Coul EL. Hepatitis C virus prevalence in The Netherlands: migrants account for most infections. Epidemiol Infect 2013;Jun;141(6):1310-7.
87. Urbanus AT, Van De Laar TJ, Geskus R, et al. Trends in hepatitis C virus infections among MSM attending a sexually transmitted infection clinic; 1995-2010. Aids 2014;28:781-90.
88. Vanhommerig JW, Stolte IG, Lambers FA, et al. Stabilizing incidence of hepatitis C virus infection among men who have sex with men in Amsterdam. J Acquir Immune Defic Syndr 2014;66:e111-5.
89. van de Laar TJ, van der Bij AK, Prins M, et al. Increase in HCV incidence among men who have sex with men in Amsterdam most likely caused by sexual transmission. J Infect Dis 2007;196:230-8.
90. Hullegie SJ, van den Berk GE, Leyten EM, et al. Acute hepatitis C in the Netherlands: characteristics of the epidemic in 2014. Clin Microbiol Infect 2015.
91. Health Council of the Netherlands. Screening risk groups for hepatitis B and C. Publication no 2016/16 2016.
92. van de Laar TJ, Paxton WA, Zorgdrager F, Cornelissen M, de Vries HJ. Sexual transmission of hepatitis C virus in human immunodeficiency virus-negative men who have sex with men: a series of case reports. Sex Transm Dis 2011;38:102-4.
93. McFaul K, Maghlaoui A, Nzuruba M, et al. Acute hepatitis C infection in HIV-negative men who have sex with men. J Viral Hepat 2015;22:535-8.
94. Dutch HIV Guideline: HIV Richtlijn NVHB. http://wwwnvhbnl/richtlijnhiv/indexphp/Hoofdpagina March 2018, accessed July 20th 2018.

95. Dutch National Institute for Public Health and the Environment (RIVM). Het consult seksuele gezondheid, Draaiboek 6 Testbeleid. . Available from: https://lcirivmnl/draaiboeken/consult-seksuele-gezondheid November, 2016. Accessed at July 20th 2018.
96. Rauch A, Rickenbach M, Weber R, et al. Unsafe sex and increased incidence of hepatitis C virus infection among HIV-infected men who have sex with men: the Swiss HIV Cohort Study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2005;41:395-402.
97. Stolte IG, Dukers NH, Geskus RB, Coutinho RA, de Wit JB. Homosexual men change to risky sex when perceiving less threat of HIV/AIDS since availability of highly active antiretroviral therapy: a longitudinal study. AIDS (London, England) 2004;18:303-9.
98. van der Helm JJ, Prins M, del Amo J, et al. The hepatitis C epidemic among HIV-positive MSM: incidence estimates from 1990 to 2007. Aids 2011;25:1083-91.
99. van de Laar T, Pybus O, Bruisten S, et al. Evidence of a large, international network of HCV transmission in HIV-positive men who have sex with men. Gastroenterology 2009;136:1609-17.
100. Chan DP, Sun HY, Wong HT, Lee SS, Hung CC. Sexually acquired hepatitis C virus infection: a review. Int J Infect Dis 2016;49:47-58.
101. Ghisla V, Scherrer AU, Nicca D, Braun DL, Fehr JS. Incidence of hepatitis C in HIV positive and negative men who have sex with men 2000-2016: a systematic review and meta-analysis. Infection 2017;45:309-21.
102. Azevedo TC, Zwahlen M, Rauch A, Egger M, Wandeler G. Hepatitis C in HIV-infected individuals: a systematic review and meta-analysis of estimated prevalence in Africa. J Int AIDS Soc 2016;19:20711.
103. Hullegie SJ, van den Berk GEL, Leyten EMS, et al. Acute hepatitis C in the Netherlands: characteristics of the epidemic in 2014. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2016;22:209.e1-.e3.
104. SHM. HIV Monitoring Report. 2017, accessed at 24th July 2018.
105. Matthews GV, Pham ST, Hellard M, et al. Patterns and characteristics of hepatitis C transmission clusters among HIV-positive and HIV-negative individuals in the Australian trial in acute hepatitis C. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2011;52:803-11.
106. Fierer D KY, Hare B,. Molecular epidemiology of incident HCV infection in HIV-infected MSM in the US vs infections in Europe and Australia. Abstract number 112 18th Conference on Retroviruses and Opportunistic Infections, February 27–March 2, 2011, Boston, USA.
107. Pasquier C, Bujan L, Daudin M, et al. Intermittent detection of hepatitis C virus (HCV) in semen from men with human immunodeficiency virus type 1 (HIV-1) and HCV. J Med Virol 2003;69:344-9.
108. Danta M, Brown D, Bhagani S, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. Aids 2007;21:983-91.
109. Vanhommerig JW, Lambers FA, Schinkel J, et al. Risk Factors for Sexual Transmission of Hepatitis C Virus Among Human Immunodeficiency Virus-Infected Men Who Have Sex With Men: A Case-Control Study. Open Forum Infect Dis 2015;2:ofv115.
110. Apers L, Vanden Berghe W, De Wit S, et al. Risk factors for HCV acquisition among HIV-positive MSM in Belgium. J Acquir Immune Defic Syndr 2015;68:585-93.

Part A

Optimization of hepatitis C treatment in the era of direct-acting antiviral therapy



Chapter 2

8 weeks of sofosbuvir/ledipasvir is effective in DAA-naive non-cirrhotic HCV genotype 4 infected patients (the HEPNED-001 study)

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Introduction

In contrast to genotype 1, genotype 4 hepatitis C (HCV) infections are more often found in Central Africa and the Middle East with the highest prevalence in Egypt [1]. As the initial budget impact of HCV treatment with direct-acting antivirals (DAAs) can be substantial for countries with a high HCV prevalence[2], shortening treatment duration could help in reaching WHO's HCV elimination goals[3] by lowering costs and expanding access[4]. The most recent EASL guideline suggests 8 weeks of therapy with sofosbuvir/ledipasvir (SOF/LDP) as an option for treatment-naive non-cirrhotic patients with chronic HCV of the genotypes 1a and 1b[5].

Although the first clinical trials with DAA's were primarily focused on HCV genotype 1 infections, the advent of pan-genotypic DAA's give us the opportunity to study new treatment options and even treatment shortening for genotype 4 infections[4]. Indeed, LDV showed a high potency in a study that assessed the phenotypic susceptibility of various genotype 4 subtypes[6] and in the study that led to the registration of 12 weeks of SOF/LDV for genotype 4, 41 of the 44 (93%) patients had a sustained virological response (SVR)[7]. Given the very comparable cure rates after 12 weeks of SOF/LDP for genotype 1 and 4, a treatment duration of 8 weeks may be appropriate for genotype 4 as well[8]. Recently, this approach was studied in Egyptian patients and a cure rate of 95% (41/43) was observed in the 43 patients[9]. However, these patients were HIV-negative and because genotype 4a is the most prevalent HCV subtype in Egypt, these results cannot be translated to other genotype 4 subtypes[1].

We evaluated the effectiveness of 8 weeks SOF/LDP for genotype 4 HCV-infected DAA-naive HIV-positive and -negative patients without cirrhosis in a single arm prospective open label study in 10 centers in the Netherlands and Belgium and found a high effectiveness these patients.

Methods

Design & subjects

This study was designed as a single arm prospective open label multicenter study in HIV and/or hepatitis C treatment centers in the Netherlands (n=9) and Belgium (n=1). Eligible participants were HIV positive or negative adults (≥18 years), chronically infected with genotype 4 HCV with a screening HCV RNA load <10 million IU/mL. A chronic hepatitis C infection was defined according to the EASL guideline as the presence of both anti-HCV antibodies and HCV RNA for more than 6 months[10]. Patients with an eGFR < 30 mL/min or a history of DAA treatment failure for the current episode of HCV infection were excluded. Only patients with a liver biopsy with a METAVIR score lower than AxF4 or a liver stiffness measurement (Fibroscan®) <12.5 kPa were eligible[11]. Biopsy or shear wave elastography results were allowed to be 24 months old. However, in case of METAVIR score F3 or shear wave elastography result >9,5 kPa[11], results could not be older than 12 months. All concomitant co-medication (e.g. cART) was reviewed for drug-drug interactions with the Hepatitis Drug Interactions tool of the University of Liverpool[12] and co-medication was changed if needed before DAA initiation.

Treatment & assessments

All subjects received 8 weeks of SOF/LDP 90/400 mg QD. HCV RNA loads during therapy were analyzed according to local hospital policy, but at least at baseline and week 20 (SVR12). Because SOF/LDP is already EMA-approved, there was no mandatory reporting of minor side effects during this study, but serious adverse events were registered.

Primary outcome and secondary outcomes

The primary efficacy outcome was the sustained virological response 12 weeks after the end of the 8 week therapy (SVR12) in the on-treatment (OT) study population. SVR12 was defined as an HCV RNA below the limit of detection 12 weeks or later after the end of therapy. The OT population was defined as all patients that had completed the 8-week

course and of which a HCV RNA was measured at ≥12 weeks after the end of therapy. Secondary outcomes included SVR12 in the intention-to-treat (ITT) population defined as all patients that initiated study drugs, SVR12 in the HIV positive compared to the HIV-negative population and SVR12 in the study population with baseline viral loads < 6 million IU/ml HCV RNA.

Treatment failures

HCV relapse was defined as reoccurrence of the HCV virus with which the patient was infected at the start of therapy after treatment discontinuation and after the documentation of a previously undetectable HCV RNA during therapy. However, as reinfection is frequently observed in HIV+ MSM[13] and, in 2017, approximately 35% of all acute HCV infections in Dutch and Belgian HIV+ MSM were of the genotype 4[14], it is important to differentiate reinfection from relapse because an HCV reinfection should not be considered therapy failure. Therefore, in patients with a presumed HCV relapse, a genotype analysis with a reverse hybridizing assay (the Versant® HCV Genotype 2.0 System (LiPA)) was performed to differentiate relapse with a new HCV genotype from reinfection. If genotype 4 was again present at the time of the presumed relapse, a phylogenetic analysis was done using a fragment of the envelope E2 gene which includes the hypervariable region 1, to differentiate relapse from a genotype 4 reinfection according to the methods described by Thomas et al.[15]. Patients with a documented HCV reinfection 12 weeks after the end of therapy were not considered as treatment failures in the analysis.

Sample size

Although the study was a non-randomized single arm study and therefore not a formal non-inferiority randomized clinical trial, we estimated the appropriate sample size for the study by calculating the sample size under the assumption that the cure rate with 8 weeks of SOF/LDP would be 95% and therefore identical to what was observed after 12 weeks of SOF/LDP for chronic HCV genotype 4 in the NIAID SYNERGY[16] and the 1119 study[17] . Our hypothesis is that we can shorten therapy duration to 8 weeks without a loss of effectivity. Therefore we anticipate that the SVR after 8 weeks of therapy is a fixed 95%. We based our

95% estimate on the available results on the treatment of genotype 4 with 12 weeks of sofosbuvir/ledipasvir at the time the protocol was written in 2016; the NIAID SYNERGY study[16]. In both studies combined, an SVR was observed in 61 of the 65 patients (94%) but to be on the conservative site in our sample size calculation we used a fixed 95% SVR as comparator. We use a non-inferiority margin of 10%, which means that the lower 95% C.I. of the difference between the proportion of patients with an SVR in the intervention group and the fixed SVR of 95% should not exceed 10% (e.g. if the SVR result is 95% the difference between proportions is 0% and the 95% CI of this 0% should not exceed 10%). For the study to have 90% power to show non-inferiority under our study hypothesis, and using an alfa error of 5% a sample size of 41 is needed. (Settings are therefore 1-beta of 0,9, alfa 5%, true proportion 0,95, null hypothesis proportion 0,95 and delta 0.1.[18])

Note: Although we intended to include 41 patients, as a result of the rapid treatment uptake of DAAs in HIV-infected MSM in the Netherlands and Belgium[19], the inclusion of additional patients was not possible because after the screening of 63 and the treatment of 40 HCV genotype 4 patients (of whom 30 were HIV co-infected), no eligible patients were left in any of the participating centers.

Interim analysis and statistical analysis

A single interim safety analysis was planned and performed after 10 patients had reached the SVR12 evaluation endpoint. The stopping rule in the protocol said that the study would be discontinued if <8 of the first 10 patients had an SVR12 because the upper limit of the 95% C.I. of an SVR12 of 7/10 is 89% and with current DAA therapies we considered a SVR12 <90% as unacceptably low. Data was analyzed using IBM SPSS statistics® v21. Baseline characteristics between HIV-negative and HIV-positive patients were compared with Fisher's exact test for categorical variables and 2-sided Mann-Whitney U test for continuous variables. A 2-sided $p<0.05$ was regarded as significant. For the primary as well as the secondary endpoints, the proportion of patients with SVR12 was calculated with a 2-sided C.I. using the exact Clopper-Pearson confidence intervals.

Ethics statement

The protocol was approved by all local medical ethics committees and registered in the Dutch Trial Register 'Nederlands Trial Register' (Trial ID NTR5729). All subjects signed informed consent.

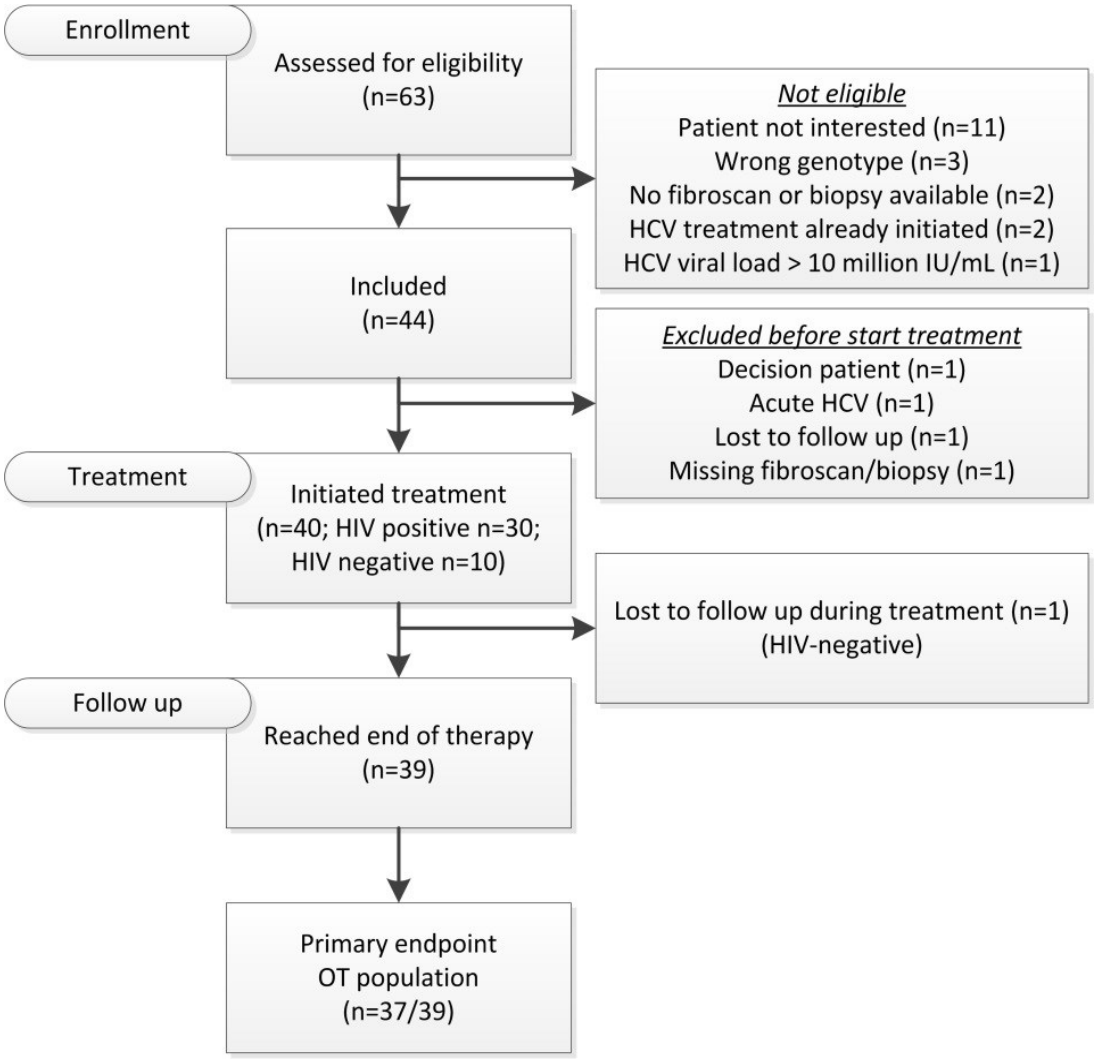


Figure 1. Flow diagram.

Results

From January 2016 until June 2017, 63 patients were screened for eligibility of which 44 were enrolled. Four patients never started therapy and 30 HIV-positive and 10 HIV-negative patients started treatment (figure 1). All patients completed the 8 weeks of therapy but 1 HIV-negative patient was lost to follow up before the SVR could be evaluated (last HCV viral load <15 IU/ml). In the on-treatment population, 33 of the 39 patients were HCV RNA negative 12 weeks after therapy and 6 were HCV RNA positive. However, 4 of them had a proven reinfection (figure 2). These 4 patients were all MSM and had ongoing unprotected sex, underlining the urgent need for effective interventions to decrease the risk of reinfection in this subpopulation. In total, 37 of 39 patients (95%; 95% CI 83-99%) of the on-treatment population were successfully treated for the HCV virus that was present at baseline. Stratified to HIV-status, 28 of the 30 HIV-positive patients (93%; 95% CI 80-99%) and 9 of the 9 HIV-negative patients (100%) reached SVR12 (p=1.0) (table 1). In the 2 treatment failures the baseline HCV viral loads were 9.8E5 and 8.7E6 IU/mL. The subtype was 4c in one patient, but in the other patient the subtype was not typable. No resistance associated mutations in NS5a or NS5b were detected at the time of HCV relapse.

Discussion and conclusion

As a result of the rapid treatment uptake of DAAs in HIV-infected MSM in the Netherlands and Belgium[19], the inclusion of additional patients was not possible because after the screening of 63 and the treatment of 40 genotype 4 patients, no eligible patients were left in any of the participating centers. Therefore, we did not reach the intended sample size of 41 patients as stated in the protocol of our study (as described supplement 1). However, although relatively small, our sample size was comparable to the number of patients included in phase III trials of SOF/LDP that led to the registration of 12 weeks SOF/LDP therapy for HCV genotype 4[5].

Our study showed that 8 weeks of LPD/SOF could be an effective therapy for non-cirrhotic HCV genotype 4 infected patients with a HCV RNA load <10 million IU/ml and is the first to

evaluate the efficacy of 8 weeks of SOF/LDP in a substantial number of HIV-coinfected patients. Our results further strengthen the observation made among Egyptian mono-infected patients[9]. Therefore, 8 weeks of SOF/LDP could be considered a treatment option in DAA-naïve genotype 4 patients without cirrhosis, thereby expanding access to therapy to a larger number of patients.

Table 1, part 1. Baseline characteristics according to HIV-status.

MSM: men who have sex with men. IVDU: intra-venous drug use. HCV: hepatitis C virus. cART: combined antiretroviral therapy. OT: on-treatment. NA: not applicable.[a]T-test. [b]Fisher's exact test. [c]2-sided Mann Withney U test. [d]Reinfections are not considered treatment failure. [e]2-sided Clopper Pearsons confidence interval.

		All (n=40)	HIV-positive (n=30)	HIV-negative (n=10)	p-value
Baseline characteristics					
Age (years)[a]	Mean +-SD	51 (+-9.9)	51 (+-10.4)	51 (+-8.7)	p=0.971
Male[b]	%, n	85% (34/40)	86,7% (24/30)	80% (8/10)	p=1.000
Caucasian[b]	%, n	80% (32/40)	76,7% (23/30)	90% (9/10)	p=0.653
Transmission mode HCV[b]					p=0.068
MSM	%, n	52.5% (21/40)	63.3% (19/30)	20% (2/10)	
IVDU	%, n	12.5% (5/40)	10% (3/30)	20% (2/10)	
Other	%, n	7.5% (3/40)	6.7% (2/30)	10% (1/10)	
Missing	%, n	27.5% (11/40)	20% (6/30)	50% (5/10)	
Previous treatment[b]					p=0.011
Naive (no treatment)	%, n	80% (30/40)	83,3% (25/30)	70% (7/10)	
Peg-interferon +-ribavirin	%, n	20% (8/40)	16.7% (5/30)	30% (3/10)	
Baseline viral load (IU/mL)[c]	Median + IQR	1.05 E6 (3.36 E5 - 3.64 E6)	1.21 E6 (3.97 E5 – 3.37 E6)	6.9 E5 (1.75 E5 – 2.00 E6)	p=0.235
Time since diagnosis of HCV infection (years)[c]	Median + IQR	4.2 (2.1-9.8)	4.4 (2.8-10.1)	4.4 (4.0-4.9)	

Table 1, continued. Baseline characteristics and outcome according to HIV-status.

MSM: men who have sex with men. IVDU: intra-venous drug use. HCV: hepatitis C virus. cART: combined antiretroviral therapy. OT: on-treatment. NA: not applicable.[a]T-test. [b]Fisher's exact test. [c]2-sided Mann Withney U test. [d]Reinfections are not considered treatment failure. [e]2-sided Clopper Pearsons confidence interval.

		All (n=40)	HIV-positive (n=30)	HIV-negative (n=10)	p-value
Baseline characteristics					
HCV Subtype[b]					p=0.304
4a	%, n	15% (6/40)	10% (3/30)	30% (3/10)	
4c	%, n	2.5% (1/40)	3.3% (1/30)	0%	
4d	%, n	37.5% (15/40)	40% (12/30)	30% (3/10)	
4t	%, n	2.5% (1/40)	0%	10% (1/10)	
Unknown	%, n	42.5% (17/40)	46.6% (14/30)	30% (3/10)	
Liver stiffness measurement (Fibroscan®)					
pKa[c]	median + IQR	5.6 (4.5-7.6)	5.3 (4.2-6.8)	8.8 (6.5 – 10.8)	p=0.004
f3 (>9.5 kPa)[b]	%, n	15% (6/40)	3.3% (1/30)	50% (5/10)	p=0.002
CD4 cell count (cells/µl)					
Nadir	Mean +-SD	NA	397.9+-53.9	NA	
at start of HCV therapy	Mean +-SD	NA	807.0+-69.0	NA	
On cART	%, n	NA	100% (30/30)	NA	
HIV viral load <40 copies/ml at start of HCV therapy	%, n	NA	97% (29/30)	NA	
Outcomes in on-treatment population[d]					
Effectiveness OT population					
%, n		95% (37/39)	93% (28/30)	100% (9/9)	
95% exact CI[e]		83-99%	80-99%	-	
HCV RNA negative 12 weeks after therapy		33	24	9	
HCV RNA positive 12 weeks after therapy					
Reinfection (genotype switch)		1	1	-	
Reinfection (phylogenetically distinct genotype 4 virus)		3	3	-	
Relapse		2	2	-	

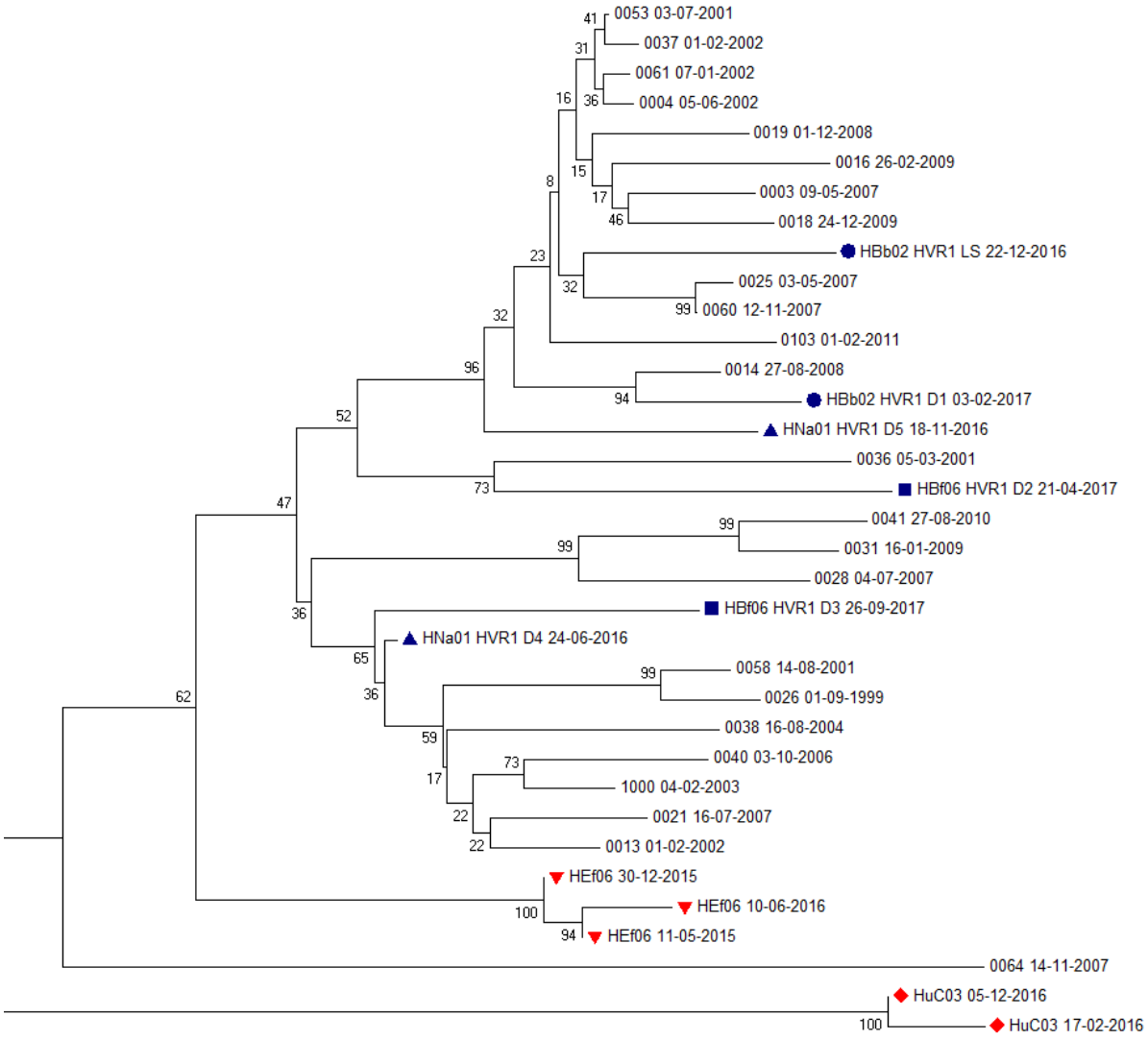


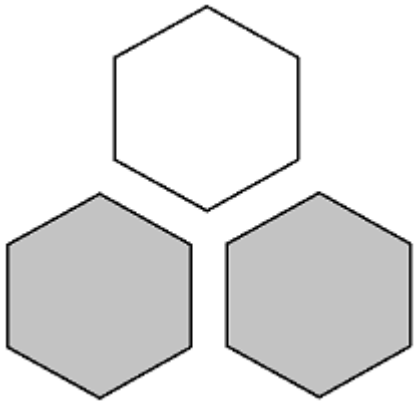
Figure 2. Evolutionary relationships of patients infected with HCV genotype 4.

Phylogenetic tree of genotype 4 sequences, including relapsers and patients with a reinfection with the same genotype before and after treatment. Relapsers are presented by filled symbols in red and reinfections are presented by filled symbols in blue. Each patient is presented by a unique symbol. The date in the labels indicate sampling dates. The evolutionary history was inferred using the Neighbor-Joining method[20]. The optimal tree with the sum of branch length = 1.30658013 is shown. The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (10000 replicates) are shown next to the branches[21]. The tree is drawn to scale, with branch lengths in the same units as those of the evolutionary distances used to infer the phylogenetic tree. The evolutionary distances were computed using the Maximum Composite Likelihood method[22] and are in the units of the number of base substitutions per site. The analysis involved 35 nucleotide sequences. All ambiguous positions were removed for each sequence pair. There were a total of 427 positions in the final dataset. Evolutionary analyses were conducted in MEGA6[23].

References

1. Abdel-Ghaffar TY, Sira MM, El Naghi S. Hepatitis C genotype 4: The past, present, and future. World J Hepatol 2015;7:2792-810.
2. Iyengar S. TTK, Vogler S., Beyer P., Wiktor S., de Joncheere K., Hill S.,. Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis. PLoS Med 2016;13:e1002032.
3. WHO Global health sector strategy on viral hepatitis 2016-2021. Available from: http://appswhoint/iris/bitstream/10665/246177/1/WHO-HIV-201606-engpdf 2017.
4. Asselah T, Hassanein T, Waked I, Mansouri A, Dusheiko G, Gane E. Eliminating hepatitis C within low-income countries - The need to cure genotypes 4, 5, 6. J Hepatol 2017.
5. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. Journal of hepatology in press.
6. Camus G, Han B, Asselah T, et al. Resistance characterization of ledipasvir and velpatasvir in hepatitis C virus genotype 4. J Viral Hepat 2018;25:134-43.
7. Abergel A, Metivier S, Samuel D, et al. Ledipasvir plus sofosbuvir for 12 weeks in patients with hepatitis C genotype 4 infection. Hepatology (Baltimore, Md) 2016;64:1049-56.
8. Llaneras J, Riveiro-Barciela M, Buti M, Esteban R. Hepatitis C virus genotype 4: Genotype 1's little brother. J Viral Hepat 2016.
9. Shiha G, Esmat G, Hassany M, et al. Ledipasvir/sofosbuvir with or without ribavirin for 8 or 12 weeks for the treatment of HCV genotype 4 infection: results from a randomised phase III study in Egypt. Gut 2018.
10. European Association for the Study of the Liver. Electronic address eee. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol 2017;66:153-94.
11. Ziol M, Handra-Luca A, Kettaneh A, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology 2005;41:48-54.
12. http://www.hep-druginteractions.org/checker.
13. Ingiliz P, Martin TC, Rodger A, et al. HCV reinfection incidence and spontaneous clearance rates in HIV-positive men who have sex with men in Western Europe. J Hepatol 2017;66:282-7.
14. Anne Boerekamps ADW, Guido van den Berk , Fanny Lauw , Mark Claassen , Dirk Posthouwer , Wouter Bierman , Sebastiaan Hullegie , Eric Florence , Anton Dofferhoff , Joop E. Arends , Bart Rijnders, . 8 weeks of grazoprevir/elbasvir for acute HCV. A multicenter clinical trial (DAHHS 2). Conference on Retroviruses and Opportunistic Infections (CROI 2018), Boston, abstract 1323, 2018.
15. Thomas X. V. GBP, Van Der Meer J. T., Ho C. K., Vanhommerig J. W., Rebers S. P., De Jong M. D., Van Der Valk M., Prins M., Molenkamp R., Schinkel J., Mosaic study group. Genetic characterization of multiple hepatitis C virus infections following acute infection in HIV-infected men who have sex with men. Aids 2015;29:2287-95.
16. Kohli A, Kapoor R, Sims Z, et al. Ledipasvir and sofosbuvir for hepatitis C genotype 4: a proof-of-concept, single-centre, open-label phase 2a cohort study. Lancet Infect Dis 2015;15:1049-54.
17. Abergel A. MS, Samuel D., Jiang D., Kersey K., Pang P. S., Svarovskaia E., Knox S. J., Loustaud-Ratti V., Asselah T. Ledipasvir plus sofosbuvir for 12 weeks in patients with hepatitis C genotype 4 infection. Hepatology 2016;64:1049-56.
18. Chow S SJ, Wang H. . Sample Size Calculations in Clinical Research, Second Edition (Chapman & Hall/CRC Biostatistics Series). 2008:Page 86, 1-Sample Non-Inferiority or Superiority.
19. Boerekamps A NAM, Smit C, Arends JE, Richter C, Reiss P, Rijnders BJ, Brinkman K, van der Valk M. High treatment uptake in HIV/HCV-coinfected patients after unrestricted access to direct-acting antivirals in the Netherlands. Clin Infect Dis 2018 Apr 17;66(9):1360-1365.
20. Saitou N. NM. The neighbor-joining method: A new method for reconstructing phylogenetic trees. Molecular Biology and Evolution 1987;4:406-425.
21. Felsenstein J. Confidence limits on phylogenies: An approach using the bootstrap. . Evolution 1985;39:783-791.

22. Tamura K. NM, and Kumar S. . Prospects for inferring very large phylogenies by using the neighbor-joining method. Proceedings of the National Academy of Sciences (USA) 2004;101:11030-11035.
23. Tamura K. SG, Peterson D., Filipski A., and Kumar S. MEGA6: Molecular Evolutionary Genetics Analysis version 6.0. Molecular Biology and Evolution 2013;30: 2725-2729.



Chapter 3

Treatment of acute hepatitis C genotypes 1 and 4 with 8 weeks of grazoprevir plus elbasvir (DAHHS 2): an open-label, multicentre, single-arm, phase 3b trial

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Research in context

Evidence before this study and added value of this study

To identify clinical trials regarding direct-acting antivirals for acute hepatitis C we searched PubMed for clinical trials using the search terms 'hepatitis C' and 'acute' and published since 2008 as well as the trial registries clinicaltrials.gov and clinicaltrialsregister.eu and conference abstracts of all major hepatology and HIV conferences. We excluded clinical trials with interferon-based regimens. The first clinical trials with 6 or 12 weeks of sofosbuvir and ribavirin for acute hepatitis C genotype 1 showed only moderate results with cure rates between 32-59%. More recently, trials with 6 to 8 weeks of combination DAA therapy for acute hepatitis C showed cure rates between 77-100%. However, given the low number of patients in each of the studies (n=20-30) and the fact that almost all patients were infected with genotype 1 only, no definite conclusions could be drawn. To our knowledge, the DAHHS2 study is the first study that included a sufficient number of patients (n=80) to demonstrate that a short 8-week regimen of grazoprevir and elbasvir is an effective therapy for patients with an acute hepatitis C of both the genotypes 1 and 4. Indeed, 99% of the patients were cured which is comparable to the success observed when a longer (12 weeks) treatment is given to patients with chronic hepatitis C infection of the same genotypes.

Implications of all available evidence

In specific populations at risk of onward hepatitis C transmission to others (e.g. transmission to sex partners in men having sex with men or to needle sharing partners in people who inject drugs) being able to start curative hepatitis C therapy immediately after the diagnosis of an acute hepatitis C infection will not only prevent transmission to others but will lead to direct (shorter treatment duration is possible) and indirect (new infections prevented) cost savings. As our study shows that treatment of hepatitis C infection with grazoprevir and elbasvir is effective in the acute phase of infection, this treatment strategy should be considered in populations with a high risk of onward hepatitis C infection.

Abstract

Background

Direct-acting antivirals effectively cure chronic HCV but definite data on their efficacy when used during the acute phase of HCV infections are lacking. In patients at continued risk of transmitting HCV to others, being able to treat *acute* HCV immediately after diagnosis will prevent onward transmission. We studied grazoprevir/elbasvir (G/E) as *acute* HCV therapy to evaluate its efficacy and to prove that treatment can be shortened during the *acute* phase of infection.

Methods

Single-arm prospective trial on the treatment of *acute* HCV in 15 centres in the Netherlands and Belgium (*NCT0260032)*. Patients (≥18 years) were included if they had an acute HCV genotype 1 or 4 infection that was ≤26 weeks old. Treatment with 8 weeks of G/E 100/50mg daily was initiated no later than 6 months after infection with an HCV genotype 1 or 4. The primary endpoint was sustained virological response (SVR) in all patients who started treatment. The 93% SVR observed in the phase III study of 12 weeks of G/E for *chronic* HCV was used as comparator with a 10% non-inferiority margin. Here we present the final results of the study.

Findings and interpretation

From 02/2016 to 03/2018, 146 patients were diagnosed with a recently acquired HCV infection, 86 were included and 80 started therapy. 79 had an SVR (99%; 95% C.I.93-100%, non-inferiority proven). Also, all 14 patients who were infected with a virus carrying a clinically significant polymorphism in NS5a were cured. If reinfections were considered treatment failures, the SVR was 94% (95%C.I. 86-98%). No related serious adverse events were seen and none of the adverse events led to study drug discontinuation. The most common adverse event was a new sexually transmitted infection (19; 24%). Eight weeks of G/E cured 99% of the acute HCV infections. Therefore, 8 weeks of G/E can be regarded as an effective treatment for acute HCV infection genotype 1 and 4.

Introduction

In 2016 the World Health organization released a global health sector strategy on viral hepatitis. One of these goals was combating hepatitis C, towards its elimination as a public health threat, and consisted of a 90% reduction in new HCV infections (incidence) and a 65% reduction of HCV-related deaths (mortality)[1].

With the advent of direct acting antivirals (DAA), this goal seems to come closer in some well-defined populations with a high HCV prevalence such as HIV-positive men who have sex with men (MSM)[2]. However, they are also one of the patient populations with the highest incidence of acute HCV infections and HCV reinfections[3,4]. Although compared to people who inject drugs, HIV positive MSM represent an intermediate prevalence and incidence group (1-1.5/100 patient years of follow-up), a subgroup with extremely risky behaviour and therefore a much higher incidence exists. Recent modelling studies as well as observational studies suggest that, as a result of the DAA-treatment as prevention effect, a systematic and nationwide treatment of chronic HCV in HIV-infected MSM could lead to a substantial decrease in the HCV prevalence as well as incidence of new HCV infections[2,5-8].

However, additional interventions are also needed if HCV elimination is to be achieved[9]. Indeed, as long as large and conclusive studies on the effectivity of DAA for acute HCV are lacking, treatment during the acute phase of the infection is often not possible due to registration and/or reimbursement restrictions. Therefore, treatment of the acute infection has to be postponed until the chronic phase. This delayed treatment approach may not only be unsatisfactory from the individual patient perspective, but also from a public health perspective, as overall healthcare costs are likely to increase due to ongoing HCV transmissions caused by this treatment delay. Indeed, modelling studies demonstrated a benefit in costs when treatment was initiated in the acute phase of the infection in patients with the risk of transmitting HCV to others[10]. If HCV could be effectively treated in the acute phase of infection among high risk patients like in HIV positive MSM, this could aid micro-elimination of HCV from this subgroup in an attempt to reach global elimination of HCV according to the WHO elimination goals[11].

For patients with chronic HCV of the genotype 1b, 8 weeks of grazoprevir/elbasvir was shown to be very effective in for patients with F0-F2 with 79/81 having an SVR12 in the STREAGER trial and a similar study is ongoing for genotype 4 infected patients[12,13]. However with an SVR of 80% (95% CI 61-92), 8 weeks of grazoprevir/elbasvir led to less favorable results for patients with a chronic infection of the genotype 1a in a phase II study[14].

In the interferon era, the treatment of HCV was much more effective when given during the first 6 to 12 months after infection even when the treatment duration was shortened substantially[15-17]. The few studies that have examined the efficacy of interferon-free DAA therapy during the acute phase of an HCV infection only included a small number of patients (n=20 to 30) and almost exclusively with a genotype 1 infection. The observed cure rates varied between 77-100%, but the studies were too small to draw any definite conclusions and were recently reviewed by Martinello et al.[18].

The Dutch Acute HCV in HIV study no. 2 (DAHHS2) evaluated the efficacy and safety of grazoprevir/elbasvir for eight weeks among people with acute genotype 1 or 4 HCV infection.

Methods

Study design and participants

This investigator-initiated trial was designed as a single-arm, prospective, open-label, multicentre phase 3b trial. Adult patients (≥ 18 years) with an acute HCV genotype 1 or 4 infection were recruited in in the Netherlands and Belgium in 15 hospitals, all of which also had an HIV outpatient clinic. All HIV treatment centres in the Netherlands and in the Dutch speaking part of Belgium were informed about the trial and invited to refer patients to one of the study sites. In all major Dutch cities, the largest HIV treatment centre participated as study site. Furthermore, the staff of all other Dutch HIV centres were informed about the study and received newsletters with contact information to facilitate referral to one of the study sites. Information about the study was posted on several websites. In Belgium the

HIV centre with the highest reported incidence of acute HCV was the study site (ITG, Antwerp) but all HIV centres could refer patients to Antwerp.

Patients were included if they had an acute HCV genotype 1 or 4 infection that was ≤26 weeks old according to the presumed day of HCV infection. An acute HCV infection was defined as a positive anti-HCV IgG or positive HCV RNA in the presence of a documented negative HCV antibody or HCV RNA test in the previous 12 months. If no documented negative test in the last 12 months was present, patients were also eligible but only if they fulfilled all of the following criteria: 1) a positive HCV RNA in association with an acute rise in ALAT >5 time the upper limit of normal with a documented normal ALAT in the previous 12 months; 2) no recent introduction of any other medication that may explain the ALAT elevation; 3) documented negative HCV IgG antibody test at any time in the past; and 4) no other explanation for ALAT elevation (e.g. Hepatitis A or E or CMV or new co-medication)[19].

The presumed day of HCV infection was calculated as the midpoint between the most recent date without any laboratory signs of an HCV infection (negative HCV test and/or normal ALAT) and the date of the first positive HCV test. Therapy was initiated no later than 26 weeks after the calculated day of HCV infection. Unless their CD4 was >500/µl without therapy, HIV infected patients had to be on cART with an HIV-RNA <400 copies/ml at the time of screening. Patients with a history of liver cirrhosis of any aetiology or patients with an untreated chronic hepatitis B (HBV) infection were excluded as well as patients with a virologically controlled HBV who had significant liver fibrosis on transient elastography (F2 or higher).

Procedures

All subjects were treated with 8 weeks of grazoprevir/elbasvir 100/50 mg given as an oral fixed drug combination tablet once daily. The decision to observe patients for possible spontaneous clearance of the HCV infection was left to the treating physician. Patients were seen in a HIV clinic at screening, baseline, week 2, 4 and 8 during therapy and 4, 12 and 24 weeks after therapy. Laboratory results of those visits were reported to the investigators by the participating study centres after each study visit. Adherence was

evaluated by pill counts during week 2, week 4 and week 8 of the study. Adverse events were collected according to the Common Terminology Criteria for Adverse Events[20] by the participating study centres and reported to the investigators after each study visit.

Outcomes

The primary efficacy endpoint was sustained virological response at post-treatment week 12 (SVR12; HCV RNA <15 IU/ml) in all patients who started treatment. HCV RNA was determined with the local standard of care HCV RNA test (TaqMan 2.0 assay (Roche Diagnostics) or Abbott Realtime M2000; lower limits of HCV RNA detection resp. 15 and 12 IU/mL). Because the incidence of HCV reinfection is high in HIV-positive MSM[2,21], patients with a documented HCV reinfection 12 weeks after the end of therapy were not considered to have treatment failure in the primary analysis as predefined in the study protocol. Reinfection was defined as the detection of a different virus at SVR12 compared to the baseline virus, either by HCV genotype switch or due to the detection of a different HCV variant of the same genotype by phylogenetic analysis using a fragment of the envelope E2 gene which includes the hypervariable region 1[22]. Subsequently, patients who were HCV RNA positive at SVR12 and in whom the same virus as at baseline was detected, were considered as treatment failure. Sequences were analysed in the context of local HCV MSM-variants[22]. Secondary endpoints were safety, SVR12 in in genotype 1 and in genotype 4 infections separately and SVR12 in all patients who started treatment in which patients lost to follow-up or who discontinued treatment for other reasons than virological failure were excluded.

Sequencing and alignment method

The genotype and the subtype of the sequences was first assessed using the Rega HCV genotyping tool[23]. Sequences classified with a particular genotype were then aligned to a reference sequence with the same genotype and trimmed to equal length. NS5A resistance-associated substitutions (RAS) were defined as all changes in amino acids in the positions 28, 30, 31, 58 and 93. In addition, at position 58 only the 58D RAS was considered relevant.

Statistical analysis

With a sample size of 80 patients and a non-inferiority margin of 10% the study would have 89% power to detect non-inferiority compared to a SVR rate of 93% observed in patients treated with 12 weeks of grazoprevir/elbasvir for chronic HCV of the genotype 1a or 4 in the phase 3 C-EDGE study[24]. Data were analysed using IBM SPSS statistics® v21. For the primary as well as the secondary endpoints, the proportion of patients with SVR12 was calculated with exact 2-sided Clopper-Pearson confidence intervals (C.I.) and non-inferiority was concluded if the lower 95% C.I. of the SVR12 was above 83%.

Ethical statement

The institutional review board of all participating centres as well as the competent authority of both countries approved the study and the study was performed in accordance with GCP standards. All subjects gave written informed consent. The protocol was registered at ClinicalTrials.gov (NCT02600325).

Role of the funding source

This investigator-initiated study was supported by a research grant to BJAR from MSD and Health-Holland. MSD also provided the study drugs. The funding sources had no role in study design, no role in the collection, analysis, or interpretation of the data and no role in the writing of the report. The corresponding author and the last author both had full access to all of the data and the final responsibility to submit for publication.

Results

Participants and baseline characteristics

Patients were recruited between February 15th, 2016, and March 2nd, 2018. In total, 146 patients with a recently acquired HCV were evaluated for eligibility of whom 86 were enrolled and 80 started therapy. Reasons for non-eligibility and not starting therapy can be found in figure 1. All patients completed the treatment period and no patients were lost to follow up. A negative HCV RNA or antibody test on plasma that had been collected and stored at the preceding HIV outpatient visit (typically 6 months earlier) led to the acute HCV diagnosis in the majority of the patients (n=72) while 8 patients fulfilled the alternative definition. Their mean age was 47 years and all patients were MSM and 90% were Caucasian (table 1). In 24% of the patients the current HCV episode was a reinfection, 64% of all patients had an HCV genotype 1a infection and 36% a genotype 4. The median baseline ALT was 139 IU/ml (IQR 74-315) and the median baseline HCV RNA was 310,000 IU/ml (IQR 34000-1,400,000). 91% of the patients were HIV-coinfected and all were on cART, with an HIV viral load <50 copies/ml in 98% of co-infected patients and a median CD4 cell count of 605/µl (IQR 490-765). Regarding the HIV-negative patients, 4 out of 7 were receiving PrEP. No HBV-coinfected patients were included. Only 2 out of the 80 patients had a symptomatic (icteric) acute hepatitis C at screening. The mean total bilirubin was 13 +-6 µmol/L and only 13 out of 80 patients had a total bilirubin above the upper limit of normal (ULN > 17 µmmol/L; max. 39 µmol/L).

Virological response

Among the 80 patients that were enrolled and started treatment, 75 (94%) were HCV RNA negative 12 weeks after the end of therapy. No patients were lost to follow up or interrupted treatment. Of the 5 patients that were HCV RNA positive at that time, the phylogenetic analysis showed that 1 patient had failed treatment while the other 4 had a reinfection with a different HCV strain (figure 2, end of chapter). Therefore, the primary endpoint was observed in 79 of the 80 patients (99%; 95% C.I, 93-100%) and this was non-inferior to the pre-defined 93% success rate. Even if the 4 HCV reinfections were

considered treatment failures, a non-inferior HCV cure rate of 94% (95% C.I. 86-98%) was observed. In the 4 cases of reinfection, HCV RNA was <15 IU/ml at the end of therapy. Therefore, it is likely that the reinfection occurred between week 8 and week 20 of the study. The genotype that was detected at the time of reinfection was genotype 1a in 3 and genotype 4 in 1 patient. The patient, in whom treatment had failed, was a 50-year-old male with a well-controlled HIV-coinfection and a genotype 4d HCV infection with a baseline viral load of 14,700,000 IU/ml. Although his HCV RNA load declined rapidly during therapy HCV RNA remained detectable at his last day of therapy (17 IU/ml). No NS3 or NS5A resistance associated variants were detected in the HCV viruses sequenced at baseline and at SVR12 time point in this patient. According to the patient and confirmed by drug accountability records treatment adherence had been perfect. Response rates were comparable within the different patient subgroups of HCV genotype 1 versus 4 (p=0.4) or HIV-positive versus negative patients (p=1.0) (table 2, figure 3). Furthermore, the impact of the baseline HCV viral load on SVR12 was evaluated and showed that all but one of the 23 patients with a baseline viral load above 1 million IU/mL had an SVR (figure 4).

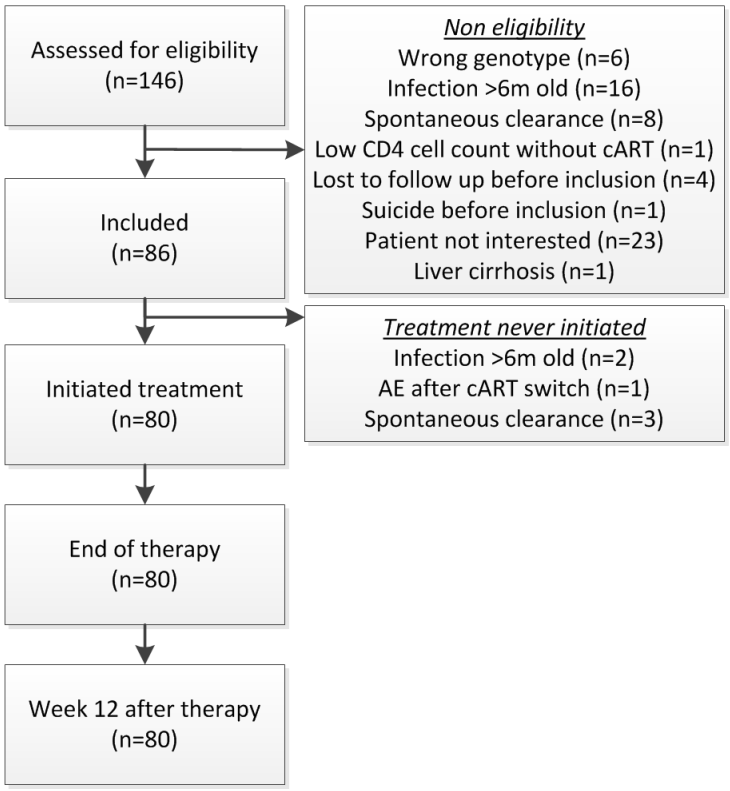


Figure 1. Flow diagram.

AE: adverse event. cART: combined antiretroviral therapy.

Table 1. Baseline demographic characteristics and characteristics of disease.

**Mean (+-SD), †Median (IQR)*

	All patients	**Genotype 1a**	**Genotype 4**
Number	80	51	29
Age – years *	47 (+-10)	47 (+-10)	49 (+-8)
Male sex – no. (%)	80 (100)	51 (100)	29 (100)
Caucasian – no. (%)	72 (90)	46 (90)	26 (90)
Transmission route HCV – no. (%)			
MSM	80 (100)	51 (100)	29 (100)
Current episode is a reinfection – no (%)	19 (24)	12 (24)	7 (24)
How many HCV episodes?			
1	61 (76)	39 (76)	22 (76)
2	15 (19)	9 (18)	6 (21)
3 or more	2 (5)	3 (6)	1 (3)
ALT – IU/ml †	139 (74-315)	144 (76-310)	136 (70-427)
HCV RNA – IU/ml †	310,000 (34,000-1,400,000)	330,000 (31,000 – 1,400,000)	250,000 (49,000 – 1,500,000)
Time between estimated infection date and HCV treatment - months *	4.4 (+-1.2)	4.3 (+-1.1)	4.6 (+-1.3)
Time between first positive HCV RNA test and HCV treatment – months *	2.0 (+- 1.0)	2.0 (+- 1.0)	2.0 (+-1.1)
HBV coinfection – no. (%)	0	0	0
HIV coinfection – no. (%)	73 (91)	46 (90)	27 (93)
CD4 cell count - /µl †	605 (490-765)	601 (497-770)	610 (396-767)
HIV viral load <50 copies/ml – no. (%)	71 (98)	45 (98)	26 (96)
Patient on cART – no. (%)	73 (100)	46 (100)	27 (100)

Baseline NS5A resistance-associated substitutions (RAS)

Of the subgroup of patients infected with HCV genotype 1a (n=51), 12 patients had a M28V substitution, of which 1 patient showed two substitutions (M28V + Y39H). One patient had a single Q30R substitution and another patient had a single Y93H substitution (figure 5). All these 14 patients reached SVR12. In the subgroup of patients infected with HCV genotype 4 (n=29) no NS5A RAS were found. The baseline viral load in patients with an NS5a mutation was 366,500 IU/ml (IQR 70,925-1,039,250 IU/ml) and comparable to the viral load in the other patients (308,944 IU/ml; IQR 45,200-1,380,000). Also, the time from diagnosis to treatment initiation was comparable (4.4+-1.0 and 4.4+-1.2 months respectively).

Table 2. Treatment outcomes, overall and according to genotype and HIV-status.

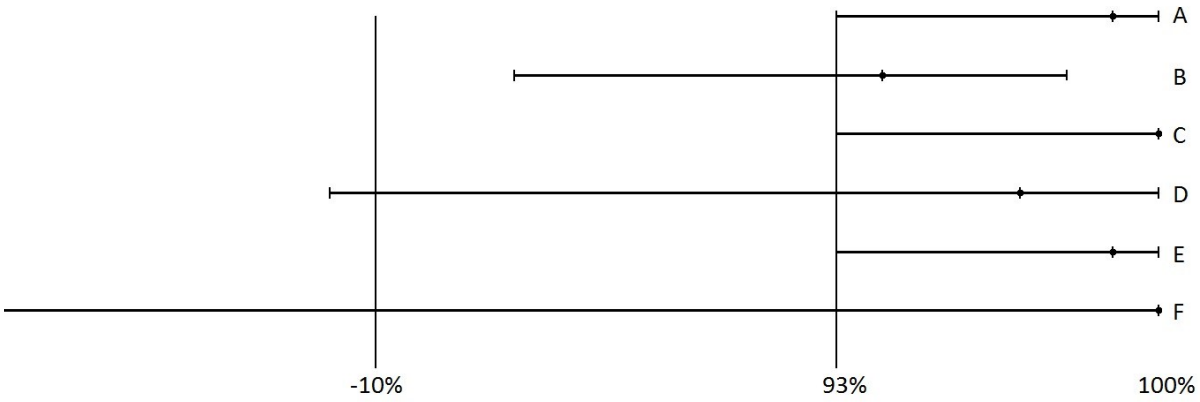
	All patients		**Genotype**		**Hiv-status**	
	A Reinfection not counted as treatment failure	**B** Reinfection counted as treatment failure	**C(*)** 1a	**D(*)** 4	**E(*)** Positive	**F(*)** Negative
Started therapy – no.	80	80	51	29	73	7
Primary endpoint – no.	80	80	51	29	73	7
SVR12 – no.	75	75	49	26	68	7
Reinfection – no.	4	4	2	2	4	0
Treatment failure– no.	1	1	0	1	1	0
Total cured – no.	79/80	75/80	51/51	28/29	72/73	7/7
% (95% exact CI)	99% (93-100)	94% (86-98)	100% (93-100)	97% (82-100)	99% (93-100)	100% (59-100)

A: all patients (n=80), reinfection is not counted as therapy failure (primary endpoint). B: all patients (n=80), reinfection is counted as failure. C: patients with genotype 1a infection (n=51). D: patients with genotype 4 infection (n=29). E: HIV positive patients (n=73). F: HIV negative patients (n=7). CI: confidence interval. (*) In group C, D, E and F reinfections are not counted as treatment failure.

Drug-drug interactions between the study regime and cART

At screening, 27 of the 28 patients on a HIV regimen susceptible to drug-drug interactions with grazoprevir/elbasvir were successfully switched to a compatible cART regimen. This included 8 patients on elvitegravir/cobicistat, 8 on efavirenz, 6 on nevirapine and 5 on darunavir/ritonavir.

Figure 3. Treatment outcome in relation to the non-inferiority margin of 10%.



A: all patients (n=80), reinfection not counted as therapy failure (primary endpoint). B: all patients (n=80), reinfection counted as failure. C: patients with genotype 1a infection (n=51). D: patients with genotype 4 infection (n=29). E: HIV positive patients (n=73). F: HIV negative patients (n=7).

Figure 4. Baseline HCV viral load (IU/ml) according to treatment outcome.

Black: sustained virological response 12 weeks after therapy. Grey: reinfection. White: treatment failure.

Adherence and safety

Based on pill-count, the adherence during the 8 weeks of treatment was 95%. The few patients that had not finished the 56 pills at the end of week 8 took the remaining pills in week 9. The study regimen was generally well tolerated; 59 of 80 patients (74%; 95% C.I. 63-82%) reported at least one adverse event (table 3b) of which 66% were considered mild in severity by the investigator. No related serious adverse events were seen and none of the adverse events led to study drug discontinuation (table 3a). The most common adverse event was a new sexually transmitted infection (STI), 20 different STI's were seen in 19 patients (24%). One patient was diagnosed with both Chlamydia trachomatis and syphilis during the study, 6 patients were newly diagnosed with syphilis, 4 with Chlamydia trachomatis, 3 with gonorrhoea, 2 with Lymphogranuloma venereum, 1 with scabies, 1 with Shigella dysentery and 1 with sexually transmitted hepatitis A. The most common reported possibly related adverse events were fatigue (11 patients; 14%), headache (7; 9%), insomnia (7; 9%), mood changes (5; 6%), dyspepsia (5; 6%), concentration impairment (4; 5%) and dizziness (4; 5%). Of note, one patient was screened but eventually did not initiate study medication because he had a (non-serious) adverse event after a switch in the cART regimen, as his prior cART regimen was incompatible with grazoprevir/elbasvir.

Figure 5. Proportion of NS5A RAS in patients infected with HCV genotype 1a.

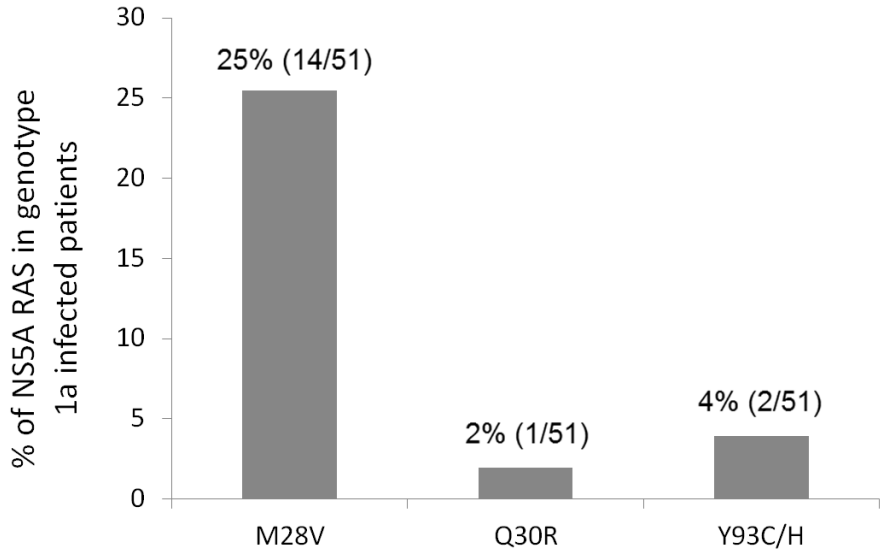


Table 3a. Mortality, serious adverse events and any adverse events

	All patients (n=80)
Death – no. (%)	0
Serious adverse event – no. (%)	
Traumatic rectal bleeding – no. (%)	1 (1)
Low back surgery – no (%)	1 (1)
Any adverse event – no. (%)	59 (74)

Table 3b. Most common adverse events

	All patients (n=80)
Sexual transmittable infection – no. (%)	19* (24)
Upper respiratory infection – no. (%)	15 (19)
Fatigue – no. (%)	14 (18)
Infections – no. (%)	11 (14)
Diarrhoea – no. (%)	9 (11)
Insomnia – no. (%)	9 (11)
Mood changes – mo. (%)	8 (10)
Dyspepsia– no. (%)	8 (10)
Skin disorder – no. (%)	8 (10)
Headache – no (%)	7 (9)
Dizziness – no. (%)	5 (6)
Injury – no. (%)	4 (5)
Concentration impairment – no. (%)	4 (5)
Back pain – no. (%)	4 (5)

**20 Sexual transmittable infections in 19 patients.*

Discussion and conclusion

In the largest study on the treatment of acute HCV with DAA to date, an 8-week course of grazoprevir and elbasvir cured 79 of the 80 (99%) patients diagnosed with an acute HCV of the genotypes 1a or 4. Its non-inferiority to the SVR observed for chronically infected patients treated with 12 weeks of grazoprevir and elbasvir in the phase III C-EDGE trial, convincingly demonstrates that this regimen is also effective during the acute phase of an HCV infection. Furthermore, this high cure rate was achieved using a shorter treatment duration. The treatment was very well tolerated and overall compliance was excellent. In contrast to previous studies on DAA therapy for acute HCV[25-29], the sample size of our study was sufficiently large to draw statistical conclusions about non-inferiority and our study also included a substantial number of HCV genotype 4 infections. Indeed, despite the fact that a substantial number of acute HCV infections among MSM in Europe are of the genotype 4, previous studies on DAA for acute HCV infection were almost entirely limited to genotype 1a.

Specific to the DAA regimen we studied, the grazoprevir/elbasvir label in the USA indicates that testing for NS5a polymorphisms should be pursued and treatment should be extended from 12 to 16 weeks in patients with chronic HCV genotype 1a infection with certain NS5a polymorphisms. As the relevance of NS5a polymorphisms in patients treated for an acute HCV has never been demonstrated we used a fixed 8-week treatment duration for all patients and did not test for NS5a polymorphisms before treatment initiation. All 14 patients infected with a genotype 1a that carried an NS5a polymorphism had an SVR12 after 8 weeks of therapy. This is in sharp contrast with the response rate of 70% (39/56) described in patients with a chronic genotype 1a infection treated for 12 weeks (p=0.02) if the virus carried baseline NS5A polymorphisms that led to a change of the amino acids at positions 28, 30, 31 and 93[30]. Also, we did not observe any difference in the HCV RNA kinetics during treatment of the patients with and without NS5a polymorphisms (data not shown). Therefore, our data suggest that extending the treatment duration for patients with an acute genotype 1a infection in the presence of baseline NS5a polymorphisms is unnecessary.

For HIV-coinfected patients, some of the antiretroviral drugs cannot be combined with grazoprevir/elbasvir (e.g. efavirenz or HIV-protease inhibitors) and this may limit its use in HIV positive patients. However, 27 of the 28 patients on a HIV regimen susceptible to drug-drug interactions with grazoprevir/elbasvir at the time of screening for this study were successfully switched to a compatible cART regimen. These interactions are mainly caused by the HCV protease inhibitor grazoprevir. The same interactions are observed with the 2 most recently FDA and EMA approved DAA regimens as they also both include an HCV protease inhibitor (glecaprevir as part of Maviret® and voxilaprevir as part of Vosevi®). Furthermore, the fact that 8 weeks of grazoprevir/elbasvir is by far the least expensive of all DAA regimens currently available is in favor of this regimen.

While peg-interferon was registered for the treatment of *acute* HCV when the study was designed in 2016, it is no longer used for this indication due to its numerous side-effects as well as the availability of DAA therapy for chronic HCV. Also, the SVR observed in a large phase III study on 12 weeks of grazoprevir/elbasvir for chronic HCV was available as a comparator. Therefore, we used the SVR of 93% observed in this study for patients infected with genotype 1a and 4 combined as the comparator[24]. Given the short interval between the HCV diagnosis and therapy initiation in our study of only 2 months, one may argue that a compulsory "wait for spontaneous cure" period of 2-3 months may have been preferred because it could avoid unnecessary DAA therapy. However, as DAA therapy is very well tolerated and the chances of spontaneous cure of HCV in HIV infected patients are small[31], we considered the DAA treatment as prevention effect of immediate therapy more important than avoiding unnecessary DAA therapy. Therefore, the decision to wait for spontaneous clearance was left to the treating physician. In general, physicians in the Netherlands repeat the HCV RNA measurement 4 weeks after an acute HCV diagnosis to evaluate HCV clearance before treatment is initiated. However, this was not defined in the protocol and indeed, 14 patients started therapy within 4 weeks after diagnosis. A recent modelling study that took the continued risk of onward HCV transmission to sex partners into account, showed that treating patients in the acute phase of HCV with a shorter regimen is likely to be cost-saving compared with a "wait for spontaneous cure" approach[10]. Given the fact that spontaneous clearance of HCV infections is observed less

frequently in HIV infected patients this is even more relevant for patients with HIV[21,32]. A comprehensive review on HCV elimination is available elsewhere[9].

Looking at the presence of possible predictors for spontaneous clearance in our study population, only 2 out of the 80 patients had a symptomatic (icteric) acute hepatitis C at screening and 13 out of 80 patients had a total bilirubin above the upper limit of normal. Combined with the relatively low ALT level at baseline, this illustrates that spontaneous clearance was unlikely in our study population. We did not look at IL28B genotypes in our cohort. However, in an earlier clinical trial in HIV-positive MSM in the Netherlands in 2013-2014, 25 out of 55 patients harboured the more favourable CC-genotype[15]. Whether a previous HCV infection and in particular a spontaneously cleared previous infection is an indicator of partial protective immune memory or a predictor for spontaneous clearance of a new HCV infection remains a controversial issue[33]. In our population, only 2 of the 19 patients with an earlier HCV infection in their medical history were cured without HCV therapy which illustrates the rarity of spontaneous HCV clearance in HIV positive patients.

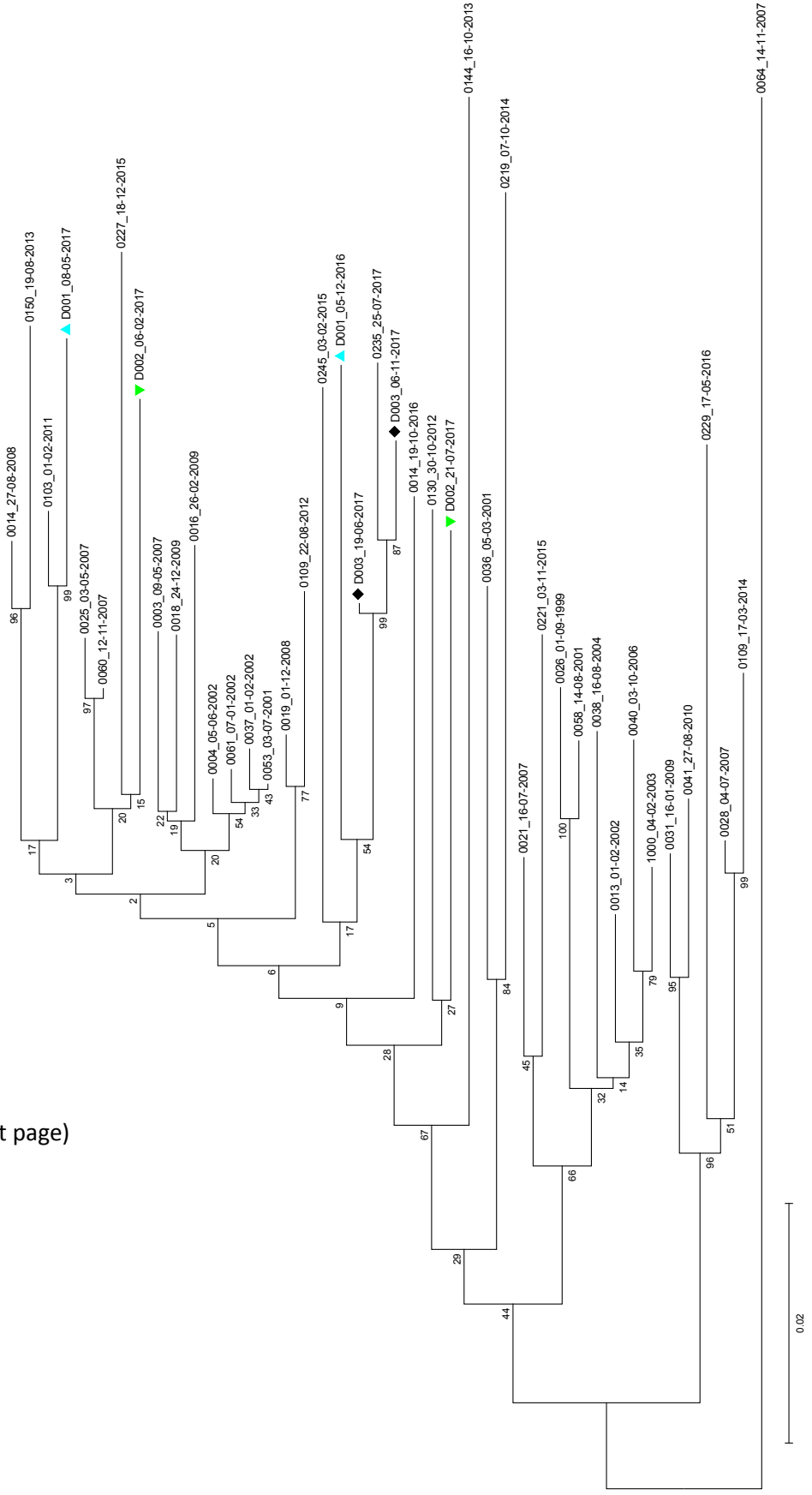
Our study has its limitations. We included a uniform study population that mostly consisted of Caucasian MSM with an HCV genotype 1a or 4 and used stringent acute HCV diagnostic criteria. This acute HCV population truly represents the patient population in which acute HCV infections are diagnosed in many European countries and in particular in the Netherlands and Belgium[2,5]. So while this may be a limitation regarding the extrapolation of the results to certain regions of the world it is not a limitation in the setting were the study was performed. Indeed, HCV transmission via injecting drug use has become rare in both countries as a result of harm-reduction interventions like needle exchange programs and opioid substitution[34]. And although the baseline HCV load of our population was lower than the typical HCV load in patients with chronic HCV, this is representative of patients with acute HCV infection.

The non-pan genotypic nature of grazoprevir and elbasvir combination may be seen as a limitation in particular in a setting where the genotyping is not possible or may lead to patients getting lost to follow-up before treatment can be initiated. In the setting where the study was performed this was not a limitation as only 6 of the 146 patients evaluated

for eligibility had a non-1 non-4 HCV genotype. Therefore, the HCV treatment spectrum of grazoprevir/elbasvir was appropriate for 96% of the patients diagnosed with an acute HCV in this setting. Furthermore, we did not collect any data on risk behaviour. Finally, the absence of a randomized control group could be seen as a limitation as well as we used a historical comparator composed of population with chronic HCV infection instead of acute HCV infection. However, the 99% cure rate does not leave much room for doubt about the efficacy of grazoprevir/elbasvir for the treatment of acute HCV.

Although, to our knowledge, we are the first to report on the non-inferiority for the treatment of acute hepatitis C infection with 8 weeks of G/E compared to 12 weeks of G/E for chronic hepatitis C infection, other clinical trials on DAA's for acute hepatitis C are currently ongoing. However, as far as we know only the REACT study (NCT02625909) will be an adequately powered non-inferiority study of a shorter (6 weeks) compared to the standard (12 weeks) treatment duration. Nevertheless, at this moment off-label use of early DAA therapy for acute HCV in patients that may transmit HCV to others is already advocated by the 2017 European AIDS Clinical Society guideline in order to prevent onward transmission[35]. The 4 HCV reinfections and 20 (other) sexually transmitted diseases diagnosed during 20 weeks of follow-up in our study clearly illustrate the continued risk behaviour and therefore risk for ongoing transmission after HCV diagnosis. Together with the observation that 24% of the patients in our study already had a history of HCV infection, this shows that not only immediate DAA therapy should be implemented on the short term but also (research on) behavioural interventions in MSM diagnosed with an acute HCV are badly needed to reduce the risk of both HCV reinfections and onward HCV transmission and enhance the possibility of micro-elimination of HCV in MSM.

In conclusion, a short 8-week grazoprevir/elbasvir regimen was highly effective for the treatment of an acute HCV genotype 1 or 4 infection.



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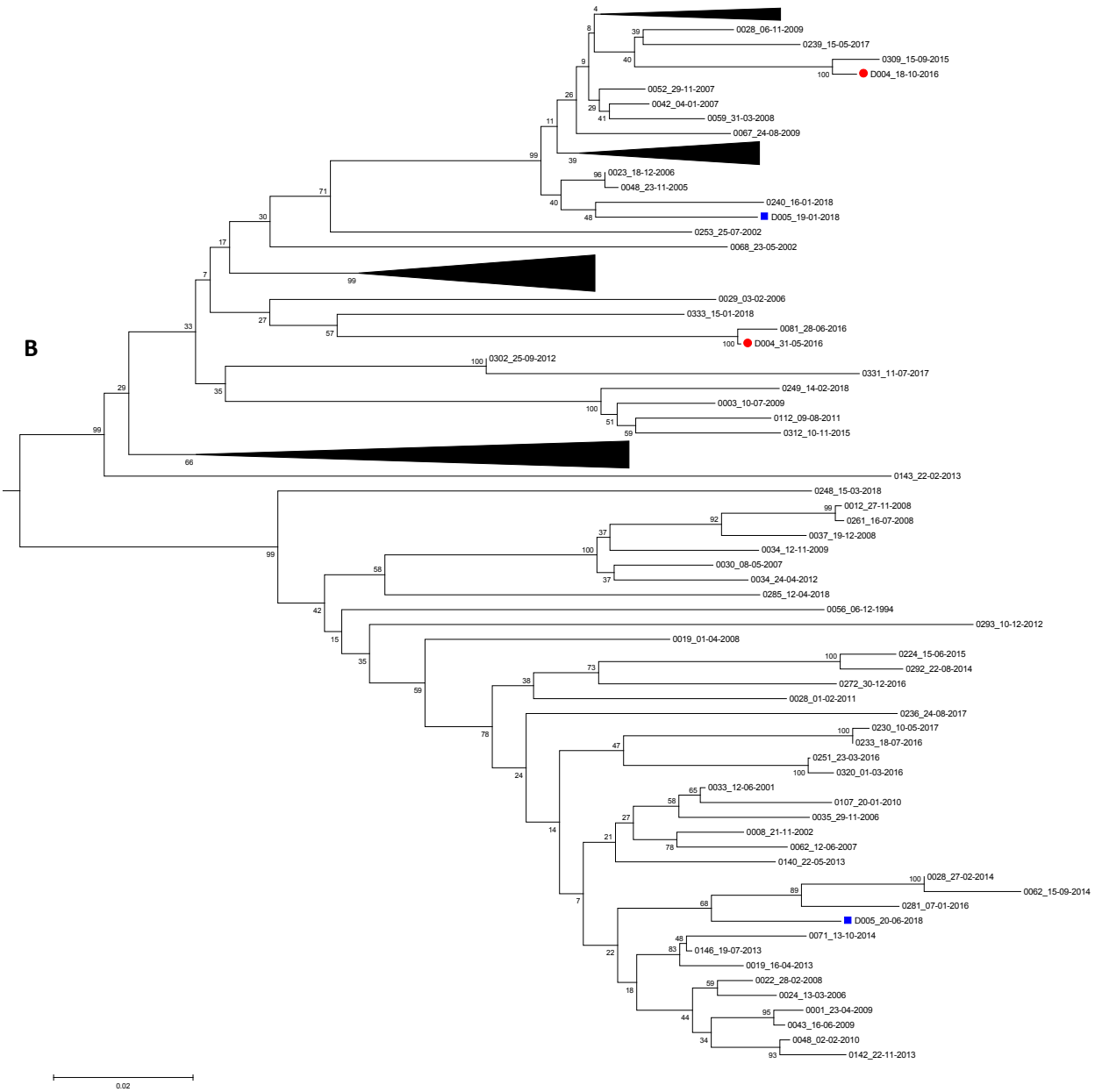


Figure 2. Evolutionary relationships of taxa, phylogenetic analysis of patients who were HCV RNA positive 12 weeks after the end of treatment.

Phylogenetic trees of local genotype 4 ***(A)*** *and genotype 1a* ***(B)*** *HCV sequences obtained from MSM[36]. Sequences of patients from this study with detectable HCV RNA 12 weeks after the end of therapy are represented by a unique colour. The tree represents the genetic distance between variants. Except for one patient, the large genetic distance for the 4 other patients shows that these patients all became reinfected with a new virus before SVR12. Sequence labels indicate the sampling date. The evolutionary history was inferred using the Neighbor-Joining method[37]. The optimal tree with the sum of branch length = 3.39563938 is shown. The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (1000 replicates) are shown next to the branches[38]. The tree is drawn to scale, with branch lengths in the same units as those of the evolutionary distances used to infer the phylogenetic tree. The evolutionary distances were computed using the Maximum Composite Likelihood method[39] and are in the units of the number of base substitutions per site. The analysis involved 137 nucleotide sequences. Codon positions included were 1st+2nd+3rd+Noncoding. All ambiguous positions were removed for each sequence pair. There were a total of 525 positions in the final dataset. Evolutionary analyses were conducted in MEGA6[40].*

References

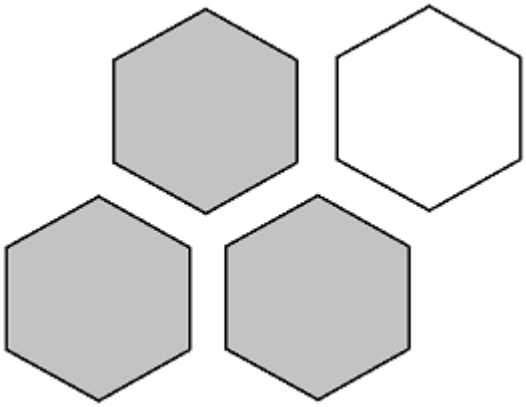
1. (WHO). WHO. Combating Hepatitis B and C to reach elimination by 2030. . Geneva: WHO; May 2016 Available from: http://appswhoint/iris/bitstream/10665/206453/1/WHO_HIV_201604_engpdf?ua=1.
2. Boerekamps A VdBG, Lauw FN, Leyten EM, Van Kasteren ME, van Eeden A, Posthouwer D, Claassen MA, Dofferhoff AS, Verhagen DWM, Bierman WF, Lettinga KD, Kroon FP, Delsing CE, Groeneveld PH, Soetekouw R, Peters EJ, Hullegie SJ, Popping S, Van de Vijver DAMC, Boucher CA, Arends JE, Rijnders BJ,. Declining HCV incidence in Dutch HIV positive men who have sex with men after unrestricted access to HCV therapy. Clin Infect Dis 2018 Apr 17;66(9):1360-1365.
3. Visser M vAF, van Oeffelen AAM, van den Broek IVF, Op de Coul ELM, Hofstraat SHI, Heijne JCM, den Daas C, Hoenderboom BM, van Wees DA, Basten M, Woestenberg PJ, Götz HM, van Sighem AI, de Hoon S, van Benthem BHB,. Sexually transmitted infections including HIV, in the Netherlands in 2016. Rijksinstituut voor Volksgezondheid en Milieu RIVM;23-Jun-2017
4. Yaphe S, Bozinoff N, Kyle R, Shivkumar S, Pai NP, Klein M. Incidence of acute hepatitis C virus infection among men who have sex with men with and without HIV infection: a systematic review. Sex Transm Infect 2012;88:558-64.
5. Boerekamps A NAM, Smit C, Arends JE, Richter C, Reiss P, Rijnders BJ, Brinkman K, van der Valk M. High treatment uptake in HIV/HCV-coinfected patients after unrestricted access to direct-acting antivirals in the Netherlands. Clin Infect Dis 2018 Apr 17;66(9):1360-1365.
6. Salazar-Vizcaya L, Kouyos RD, Zahnd C, et al. Hepatitis C virus transmission among human immunodeficiency virus-infected men who have sex with men: Modeling the effect of behavioral and treatment interventions. Hepatology 2016;64:1856-69.
7. Martin NK, Thornton A, Hickman M, et al. Can Hepatitis C Virus (HCV) Direct-Acting Antiviral Treatment as Prevention Reverse the HCV Epidemic Among Men Who Have Sex With Men in the United Kingdom? Epidemiological and Modeling Insights. Clin Infect Dis 2016;62:1072-80.
8. Dominique L. Braun BHH, Huyen Nguyen, Markus Flepp, Marcel Stoeckle, Charles Béguelin, Patrick Schmid, Julie Delaloye, Mathieu Rougemont, Enos Bernasconi, Dunja Nicca, Roger Kouyos, Jürg Böni, Huldrych F. Günthard, Jan S. Fehr. A treatment as prevention trial to eliminate hcv in hiv+ msm: The swiss hcvree trial. Oral presentation at CROI conference March 4–7, 2018, Boston, Massachusetts, abstract 81LB.
9. Martin NK, Boerekamps A, Hill AM, Rijnders BJA. Is hepatitis C virus elimination possible among people living with HIV and what will it take to achieve it? Journal of the International AIDS Society 2018;21 Suppl 2:e25062.
10. Bethea ED, Chen Q, Hur C, Chung RT, Chhatwal J. Should we treat acute hepatitis C? A decision and cost-effectiveness analysis. Hepatology 2017.
11. Lazarus JV, Wiktor S, Colombo M, Thursz M. Micro-elimination - A path to global elimination of hepatitis C. Journal of hepatology 2017;67:665-6.
12. Hezode TASPC. Efficacy and safety of 8 weeks of elbasvir/grazoprevir in HCV GT4-infected treatment-naive participants EASL 2018 - International Liver Congress Paris, France 12 April 2018 2018.
13. Asselah; AACHT. High efficacy and safety of grazoprevir and elbasvir for 8 weeks in treatment-naive, non-severe fibrosis HCV GT1b-infected patients: Interim Results of the STREAGER Study. EASL 2018 - International Liver Congress Paris, France 12 April 2018 - LBP-010.
14. Sulkowski M, Hezode C, Gerstoft J, et al. Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. Lancet (London, England) 2015;385:1087-97.
15. Hullegie SJ, Claassen MA, van den Berk GE, et al. Boceprevir, peginterferon and ribavirin for acute hepatitis C in HIV infected patients. J Hepatol 2016;64:807-12.
16. Jaeckel E, Cornberg M, Wedemeyer H, et al. Treatment of acute hepatitis C with interferon alfa-2b. N Engl J Med 2001;345:1452-7.

17. Zhang B, Nguyen NH, Yee BE, et al. Treatment of Acute Hepatitis C Infection with Pegylated Interferon and Ribavirin in Patients Coinfected with Human Immunodeficiency Virus: A Systematic Review and Meta-Analysis. Intervirology 2015;58:242-9.
18. Martinello M, Hajarizadeh B, Grebely J, Dore GJ, Matthews GV. Management of acute HCV infection in the era of direct-acting antiviral therapy. Nature reviews Gastroenterology & hepatology 2018;15:412-24.
19. Rockstroh J. Acute hepatitis C in HIV-infected individuals–recommendations from the NEAT consensus conference. AIDS 2011;25:399-409.
20. US DEPARTMENT OF HEALTH AND HUMAN SERVICES NIoH, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. May 28, 2009.
21. Ingiliz P, Martin TC, Rodger A, et al. HCV reinfection incidence and spontaneous clearance rates in HIV-positive men who have sex with men in Western Europe. J Hepatol 2017;66:282-7.
22. Thomas X. V. GBP, Van Der Meer J. T., Ho C. K., Vanhommerig J. W., Rebers S. P., De Jong M. D., Van Der Valk M., Prins M., Molenkamp R., Schinkel J., Mosaic study group. Genetic characterization of multiple hepatitis C virus infections following acute infection in HIV-infected men who have sex with men. Aids 2015;29:2287-95.
23. de Oliveira T, Deforche K, Cassol S, et al. An automated genotyping system for analysis of HIV-1 and other microbial sequences. Bioinformatics 2005;21:3797-800.
24. Zeuzem S, Ghalib R, Reddy KR, et al. Grazoprevir-Elbasvir Combination Therapy for Treatment-Naive Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis C Virus Genotype 1, 4, or 6 Infection: A Randomized Trial. Annals of internal medicine 2015;163:1-13.
25. Deterding K, Spinner CD, Schott E, et al. Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study. Lancet Infect Dis 2017;17:215-22.
26. Rockstroh JK, Bhagani S, Hyland RH, et al. Ledipasvir-sofosbuvir for 6 weeks to treat acute hepatitis C virus genotype 1 or 4 infection in patients with HIV coinfection: an open-label, single-arm trial. Lancet Gastroenterol Hepatol 2017;2:347-53.
27. Naggie S et al. 100% SVR with 8 weeks of ledipasvir/sofosbuvir in HIV-infected Men with Acute HCV Infection: Results from the SWIFT-C Trial. AASLD LiverLearning® Oct 23, 2017; ABSTRACT ID 196.
28. Fierer DS ESA, Palaniswami P,. Treatment of “acute” hepatitis C virus in human immunodeficiency virus-infected men with short-course sofosbuvir/ledipasvir. EASL LiverTree™, Apr 20, 2017; Poster presentation THU-250.
29. Martinello M, Bhagani S, Gane E, et al. Shortened therapy of eight weeks with paritaprevir/ritonavir/ombitasvir and dasabuvir is highly effective in people with recent HCV genotype 1 infection. Journal of viral hepatitis 2018;25:1180-8.
30. Elbasvir-Grazoprevir (Zepatier) Prescribing Information (FDA; reference ID 4055857), accessed on 18-09-2018.
31. Newsum AM, Schinkel J, van de Laar TJW, van der Meer JTM, Prins M. Spontaneous Clearance of Hepatitis C Virus Infection Among Human Immunodeficiency Virus-Infected Men Who Have Sex With Men. Open Forum Infect Dis 2017;4:ofx090.
32. Smith DJ, Jordan AE, Frank M, Hagan H. Spontaneous viral clearance of hepatitis C virus (HCV) infection among people who inject drugs (PWID) and HIV-positive men who have sex with men (HIV+ MSM): a systematic review and meta-analysis. BMC infectious diseases 2016;16:471.
33. Grebely J, Prins M, Hellard M, et al. Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: towards a vaccine. Lancet Infect Dis 2012;12:408-14.
34. van den Berg CH, Smit C, Bakker M, et al. Major decline of hepatitis C virus incidence rate over two decades in a cohort of drug users. Eur J Epidemiol 2007;22:183-93.
35. European AIDS Clinical Society. European Guidelines for treatment of HIV-positive adults in Europe.Version 9.0 Oktober 2017. Accessed at 16-06-2018 from www.eacsociety.org. .
36. Thomas X. V. GBP, Van Der Meer J. T., Ho C. K., et al., . Genetic characterization of multiple hepatitis C virus infections following acute infection in HIV-infected men who have sex with men. AIDS 2015;29:2287-95.

37. Saitou N. NM. The neighbor-joining method: A new method for reconstructing phylogenetic trees. Molecular Biology and Evolution 1987;4:406-425.
38. Felsenstein J. Confidence limits on phylogenies: An approach using the bootstrap. . Evolution 1985;39:783-791.
39. Tamura K. NM, and Kumar S. . Prospects for inferring very large phylogenies by using the neighbor-joining method. . Proceedings of the National Academy of Sciences (USA) 2004;101:11030-11035.
40. Tamura K. SG, Peterson D., Filipski A., and Kumar S. . MEGA6: Molecular Evolutionary Genetics Analysis version 6.0. Molecular Biology and Evolution 2013;30: 2725-2729.

Part B

Effect of HCV direct-acting antivirals and HIV pre-exposure prophylaxis on the HCV epidemic among HIV-positive MSM



Chapter 4

High treatment uptake in HIV/HCV-coinfected patients after unrestricted access to direct-acting antivirals in the Netherlands

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Clinical Infectious Diseases, 2018

Abstract

Background

The Netherlands has provided unrestricted access to direct-acting antivirals (DAAs) since November 2015. We analyzed the nationwide HCV treatment uptake among HIV/HCV-coinfected patients.

Methods

Data were obtained from the ATHENA HIV observational cohort in which >98% of HIV-infected patients ever registered since 1998 are included. Patients were included if they ever had 1 positive HCV RNA, did not spontaneously clear and were known to still be in care. Treatment uptake and outcome were assessed. When patients were treated more than once, only data of the most recent treatment episode were included. Data were updated until February 2017. In addition, each treatment center was queried in April 2017 for a data update on DAA treatment and achieved SVR.

Results

Of 23,574 HIV-infected patients ever linked to care, 1471 HCV-coinfected patients (69% men who have sex with men (MSM), 15% people who (formerly) inject drugs and 15% another HIV transmission route) fulfilled the inclusion criteria. Eighty-seven percent (1284/1471) had ever initiated HCV treatment between 2000 and 2017, 76% (1124/1471) were cured and in 6% (92/1471) DAA treatment results were pending. Among MSM 83% (844/1022) were cured and in 6% (66/1022) DAA treatment results were pending. Overall 187 patients had never initiated treatment, 14 patients failed DAAs and 54 patients failed a pegylated-interferon-alpha based regimen.

Conclusion

Fifteen months after unrestricted DAA availability the majority of HIV/HCV-coinfected patients in the Netherlands are cured (76%) or awaiting DAA treatment results (6%). This rapid treatment scale-up may contribute to future HCV elimination among these patients.

Introduction

Treatment with combinations of direct-acting antivirals (DAAs) is short, safe and highly effective in curing chronic hepatitis C virus (HCV) infection[1]. However, its high costs has led to restricted reimbursement in many countries. In the Netherlands, the first all-oral DAA regimens became available for chronic hepatitis C in June 2014, but initially only for patients with severe liver fibrosis defined as liver fibrosis stage F3 or higher. These fibrosis restrictions also applied to human immunodeficiency (HIV)-infected patients.

On the first of November 2015, the Dutch government among other countries in the world expanded the reimbursement criteria and made DAA treatment possible for all patients with chronic HCV, regardless of their fibrosis stage. Scaling up HCV treatment is one of the interventions which, combined with increased harm reduction strategies and scaling up of testing may lead to a lower HCV incidence and prevalence and eventually to HCV elimination[2,3].

Here we describe the national HCV treatment uptake in HIV/HCV-coinfected patients in the Netherlands using data from the AIDS Therapy Evaluation in the Netherlands (ATHENA) HIV observational cohort. This cohort captures data on over 98% of patients with HIV and in care in the Netherlands and is therefore highly representative of the overall Dutch HIV/HCV epidemic.

Methods

ATHENA cohort

HIV-care in the Netherlands is provided by 26 designated treatment centers. As an integral part of HIV care, the HIV Monitoring Foundation (Stichting HIV Monitoring) is responsible for prospectively collecting demographic data, relevant HIV and treatment data, as well as data on comorbidities including viral hepatitis coinfection, from HIV-infected people living in the Netherlands and receiving care in one of these treatment centers. In addition, residual plasma from HIV viral load assays is stored in each center. This data collection is known as the ATHENA cohort [4]. The ATHENA cohort was initiated in 1998 and captures data from over 98% of all patients diagnosed with HIV and in care in the Netherlands. Data collection is still ongoing and the database of the ATHENA cohort is locked and updated twice a year. This paper includes the data from the February 2017 database lock, which is 15 months following unrestricted access to DAAs in the Netherlands. Furthermore, on April 15th 2017 each center was queried about their HCV infected patients whose treatment status was uncertain, and/or whose sustained virological response (SVR) status had been pending in February 2017, in order to render data as up-to-date as possible.

Included patients and variables of interest

A patient was considered to be linked to care if he or she had visited one of the 26 HIV clinics at least once and had not opted-out to be included in the ATHENA cohort. Patients were included in the present analysis if they had at least one positive HCV RNA test and had not spontaneously cleared their HCV (HIV/HCV-coinfected patients defined as 'linked to care'). Spontaneous clearance was defined as a negative HCV RNA test following a positive HCV RNA test without initiation of HCV treatment. To label the HIV/HCV-coinfected patients who were 'retained in care' on February 1th 2017, patients were excluded if they had died, moved abroad or were lost to follow-up. Lost to follow-up was defined as the absence of a clinical visit after January 1st 2016. Included patients were assessed for age, gender, country of origin, HIV transmission route, last known CD4 cell count and HIV-1 RNA, the usage of combination antiretroviral therapy (cART), the presence of severe liver

fibrosis, the usage of any HCV treatment and the outcome of their last HCV treatment. HIV transmission route was used as a proxy for HCV transmission route. Severe liver fibrosis was defined as liver fibrosis stage Metavir F3 or higher by either liver biopsy or transient elastography result (≥9.5 kPa), based on the most recent available biopsy or transient elastography result. SVR was defined as a negative HCV RNA test at least 24 weeks after the end of HCV treatment with a pegylated interferon-alpha based regimen (SVR24) or as a negative HCV RNA test at least 12 weeks after the end of HCV treatment with DAAs (SVR12).

HCV treatment cascade

Treatment uptake and outcome were assessed using a treatment cascade. In this cascade every patient was depicted only once based on the most recent treatment the patient had received. For example, if a patient was first treated unsuccessfully with a pegylated interferon-alpha based regimen and subsequently with DAAs resulting in a SVR12, only the last treatment was accounted for in this cascade. First, the proportion of patients who had received treatment was calculated. Second, the proportion of patients who had completed any treatment was calculated. Last, the proportion of patients who reached SVR was calculated. For every step in the cascade, also the 'gap' was described (respectively the untreated patients, patients with ongoing treatment or awaiting SVR12 results and unsuccessfully treated patients).

Ethics statement and statistics

At its inception, the ATHENA cohort was approved by the institutional review board of all participating centers. Individuals can opt out after being informed by their treating physician of the purpose of data and sample collection. Data are pseudonymised and made available to investigators in a coded form. Coded data may be used for scientific purposes without further consent. For the purpose of our analysis, only existing data have been used and therefore no additional review or consent has been necessary. Chi square was used to compare categorical variables. P-values of ≤ 0.05 were considered statistically significant.

Results

Number of HIV/HCV-coinfected patients

Of 23,574 HIV patients ever registered as having been linked to care on the 1st of February 2017, 2503 had at least one positive HCV RNA test. After exclusion of patients who had spontaneously cleared their HCV (n=514), 1989 HIV/HCV-coinfected patients who had ever been linked to care remained. Of these 1989 patients, 321 patients had died (of whom 42 had a confirmed liver-related death), 83 patients had moved abroad and 114 patients were lost to follow-up (median duration of being lost to care 5 years (interquartile range (IQR) 2-11 years), resulting in 1471 coinfected patients who were still retained in care in February 2017 (figure 1), and who were included in the current analysis. Of these HIV/HCV-coinfected patients retained in care 90% were male (1325/1471) and 67% were born in the Netherlands (983/1471, table 1). The most commonly reported HIV transmission route was MSM (69%; 1022/1471), followed by a history of injecting drug use (15%; 224/1471). For the remaining 15% (225/1471) HIV transmission had occurred through another route or was unknown. HCV genotype 1 was the most prevalent (61%; 896/1471), followed by HCV genotype 4 and 3 (18% and 9%, respectively). Seventeen percent (244/1471) had liver fibrosis stage F3 or higher.

Treatment uptake and outcome

Of the included 1471 HIV/HCV-coinfected patients, 1284 had ever initiated HCV treatment between 2000 and 2017 (figure 2). Of these, 582 had been treated with an old HCV regimen (interferon-alpha, pegylated interferon-alpha +/- ribavirin +/- boceprevir or telaprevir), and 702 patients had received or were still receiving a currently used DAA-regimen (figure 3). Of those treated with DAAs, 259 (37%) were previously treated with pegylated interferon-alpha based antiviral regimens. One-hundred eighty-seven patients had never initiated any form of HCV treatment and 68 patients had failed prior HCV treatment and were still in need of retreatment. Of these 68 patients, 14 patients had failed DAAs and the remaining 54 had failed a (pegylated) interferon-alpha based regimen.

Table 1 Baseline characteristics of included patients in February 2017

	Retained in care	*Untreated*	*Ever treated*	*SVR achieved*	*Ongoing treatment/ awaiting SVR*	*Treatment failure*
Total (n)	1471	187	1284	1124	92	68
Median age at 1 Feb 2017 (IQR)	50 (44-56)	51 (43-57)	50 (44-56)	50 (44-56)	49 (42-55)	49 (46-55)
Gender (n)						
Male	1325	150	1175	1027	86	62
Female	146	37	109	97	6	6
Region of origin (n)						
Netherlands	983	102	881	775	61	45
Western Europe	161	22	139	126	9	4
Sub Saharan Africa	35	5	30	28	0	2
Caribbean/Latin America	99	20	79	69	5	5
Other	193	38	155	126	17	12
HIV transmission route (n)						
MSM	1022	72	950	844	66	40
(former) PWID	224	65	159	127	18	14
Heterosexual contact	127	35	92	81	2	9
Other/unknown	98	15	83	72	6	5
Ever used cART (n)	1454	179	1275	1118	91	66
cART regimens at HCV treatment initiation	NA	NA	422	NA	NA	NA
2 NRTI+ INI	NA	NA	412	NA	NA	NA
2 NRTI+ NNRTI	NA	NA	202	NA	NA	NA
2 NRTI + r/PI	NA	NA	128	NA	NA	NA
Other	NA	NA	120	NA	NA	NA
None						
HCV genotype (n)						
1	896	95	801	704	53	44
1a	676	59	617	548	40	29
1b	94	21	73	65	6	2
Subtype not specified	126	15	111	91	7	13
2	69	10	59	53	5	1
3	131	27	104	92	6	6
4	258	28	230	196	19	15
Other/unknown	117	27	90	79	9	2
Liver fibrosis Metavir > F3 (n)	244	25	219	192	13	14
Treatment (n)						
Currently used DAA-regimen	NA	NA	702	598	90	14
Older regimen[1]	NA	NA	582	526	2	54

[1] *interferon-alpha, pegylated interferon-alpha +/- ribavirin +/- boceprevir or telaprevir*

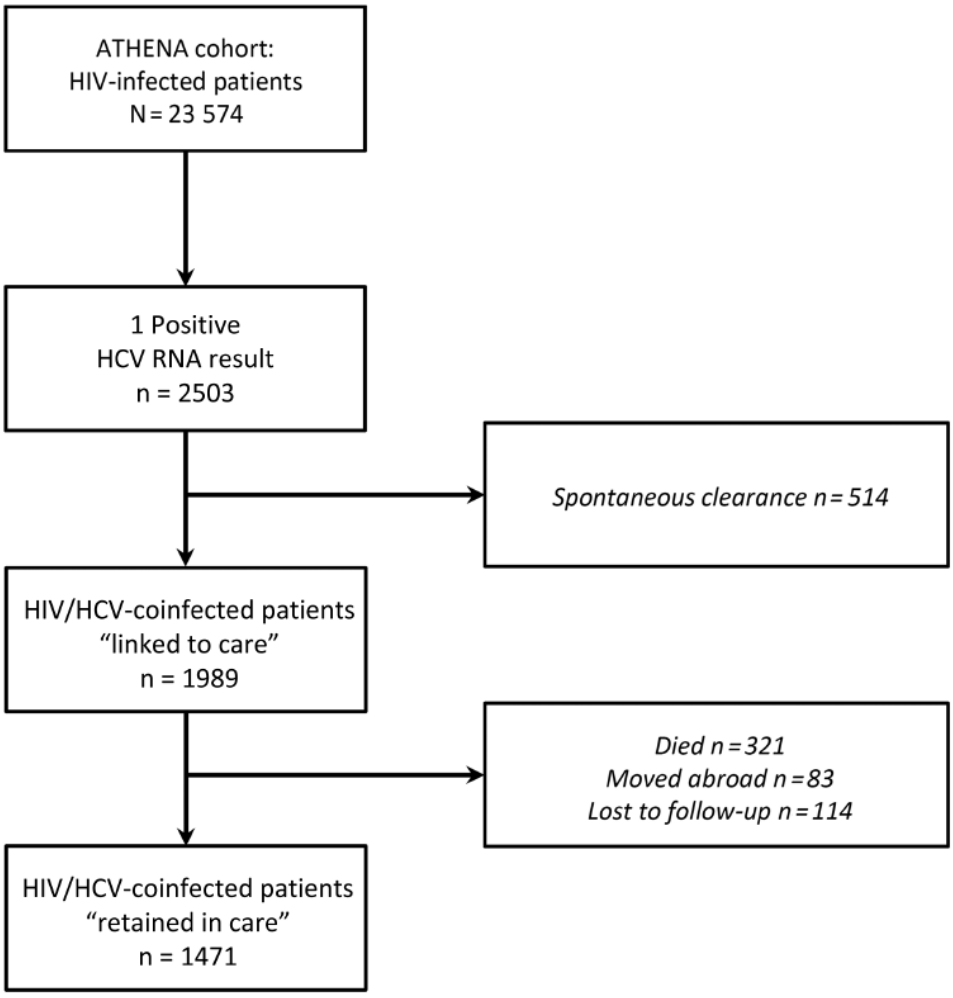


Figure 1 Flowchart of included patients

Based on their last received treatment, 1124 of the 1192 patients (94%) who were known to have completed their HCV treatment reached SVR (figure 2). When restricting the analysis to patients who were known to have completed DAA treatment, 98% of patients reached SVR12 (598/612). At the time of analysis, overall 76% (1124/1471) of the HIV/HCV-coinfected patients retained in care had reached SVR and in 6% (92/1471) DAA treatment was still ongoing or treatment results were pending. Overall only 255 patients remain to be treated. Of the 1284 patients who ever initiated treatment, 743 initiated their last treatment in 2014, 2015 or 2016. Shortly following unrestricted access to DAAs, 176, 226 and 86 patients initiated treatment in the fourth quarter (Q4) of 2015, Q1 2016, and Q2 2016, respectively, whereas in all other quarters the number of patients who initiated treatment was below 50 (figure 4).

Antiretroviral treatment during last HCV treatment

The cART regimens at the time of HCV treatment initiation are listed in table 1. Out of the 702 patients who were treated with a currently used DAA-regimen, 191 (27%) had switched cART regimen in the 3 months prior to HCV treatment initiation. For 130 of those "start of HCV treatment" was recorded in the database as reason for the cART switch, for the other 61 the reason was not explicitly recorded. Of 582 patients who were treated with an old HCV treatment regimen, 109 (19%) had switched cART regimen in the 3 months prior to HCV treatment initiation. For 54 of those "start of HCV treatment" was recorded in the database as reason for the cART switch.

Stratification by liver fibrosis stage F3-F4

Of the 244 patients classified with liver fibrosis stage F3 or higher and retained in care on the 1st of February 2017, 79% (192/244) had achieved SVR while 5% (13/244) were still undergoing DAA treatment. Thirty-nine patients with severe liver disease remain to be treated (14 patients failed previous treatment and 25 patients were never treated).

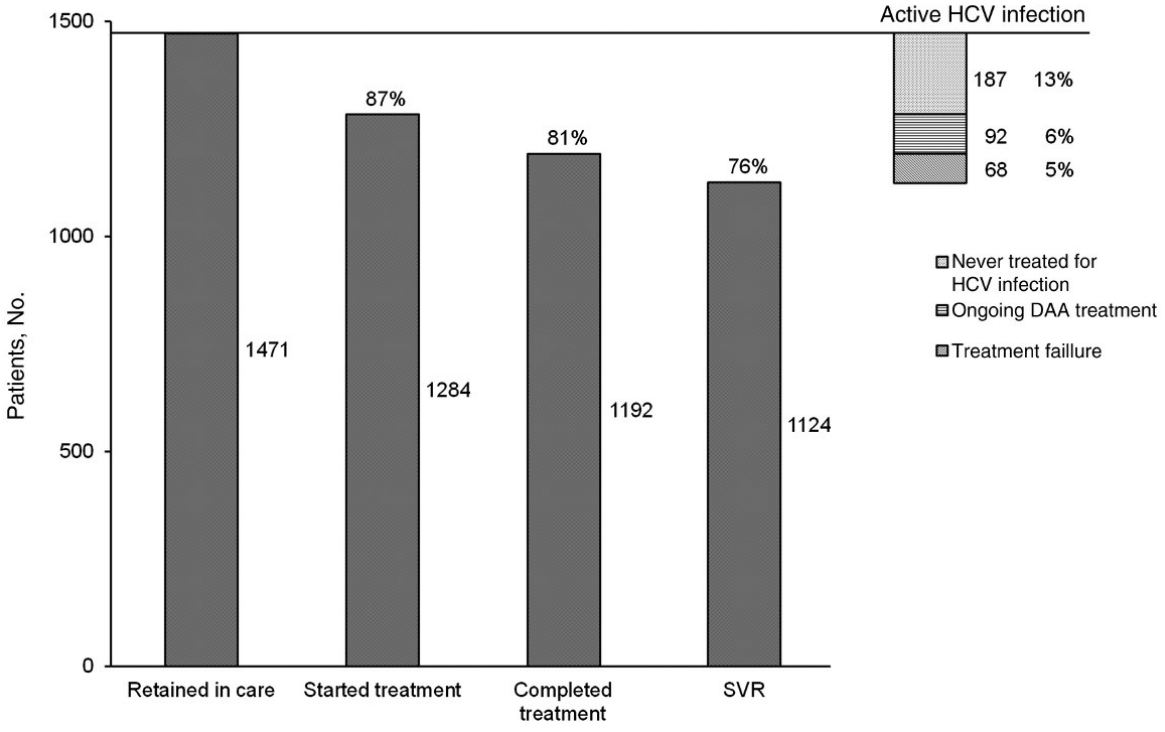


Figure 2 Treatment cascade of the Dutch HIV/HCV-coinfected population

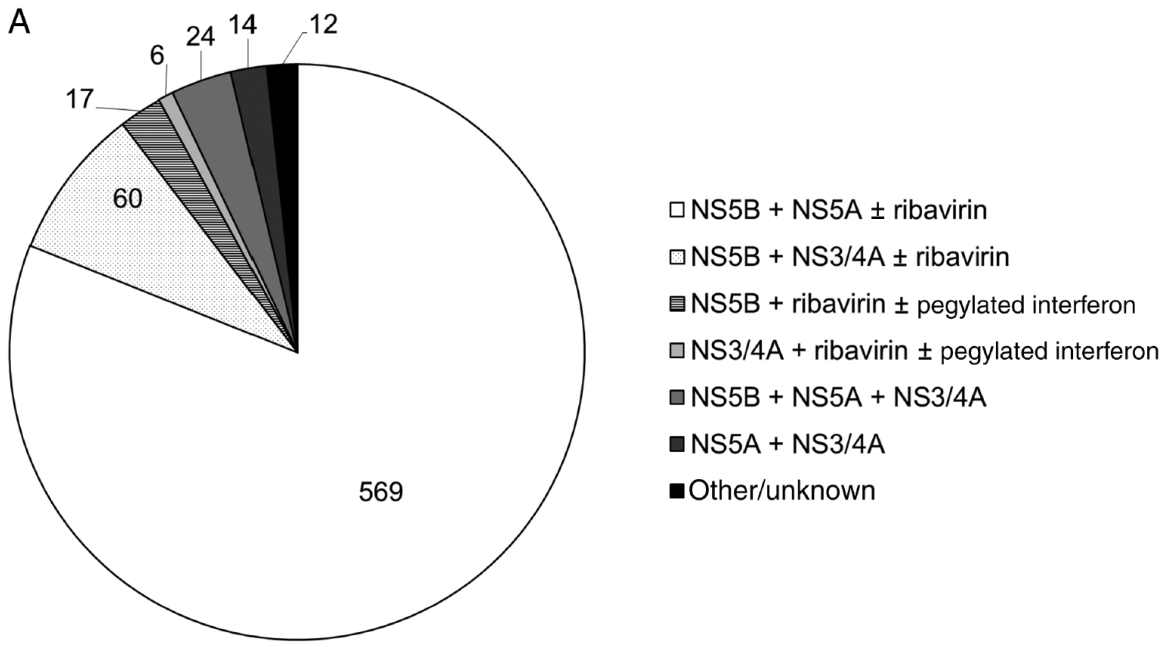


Figure 3A Used DAA regimens in the Dutch HIV/HCV-coinfected population

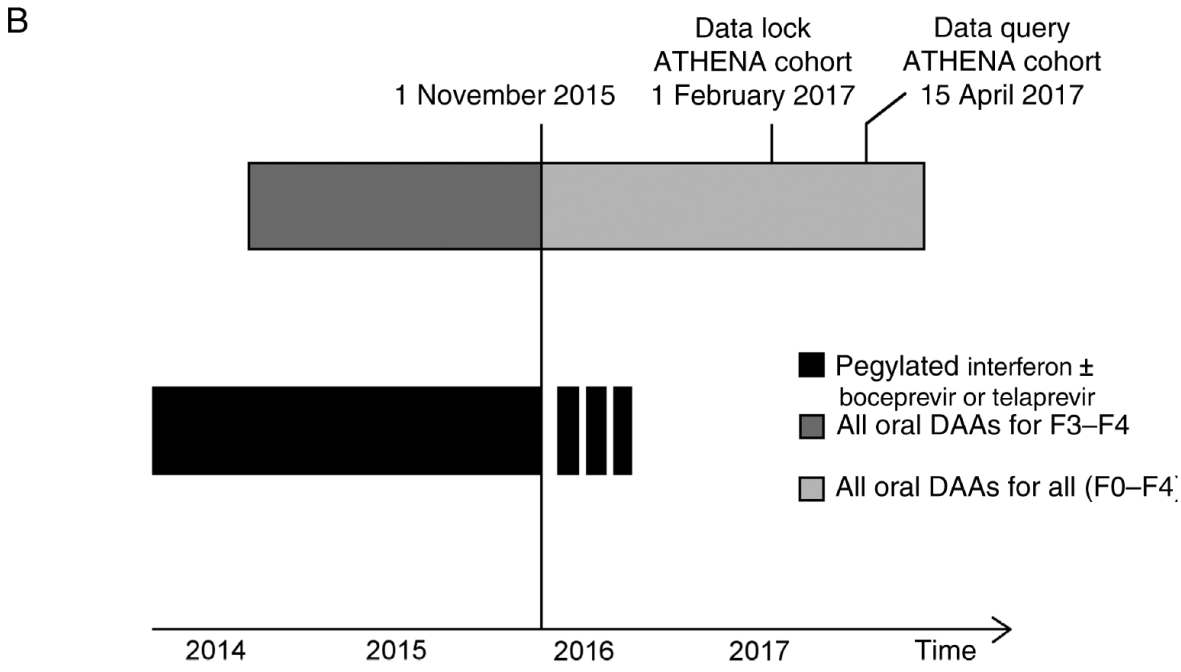


Figure 3B Schematic overview of availability of DAAs with regard to liver fibrosis stage over time

Stratification by HIV transmission route

Men who have sex with men (MSM)

1022 HIV/HCV-coinfected patients identified as being MSM were retained in care as of February 1st 2017. SVR was achieved in 83% (844/1022), which was significantly higher compared to the 76% with SVR in the overall population (p<0.001). In 6% (66/1022) DAA treatment was still ongoing or treatment results were pending. Thus, only 112 MSM remain to be treated.

People who (formerly) inject drugs (PWID)

Of the 224 HIV/HCV-coinfected patients retained in care as of February 1st 2017 and classified as (former) PWID, 57% (127/224) reached SVR, which was significantly lower compared to the overall population (p<0.001). In 8% (18/224) DAA treatment was still ongoing or treatment results were pending.

Characteristics of patients who never initiated treatment

In the patients who never initiated treatment (n=187) the proportion of women was significantly higher compared to the proportion in the patients who ever received treatment (n=1284) (20% versus 8%; p<0.001). The proportion of MSM was lower (39% versus 74%, p<0.001) and the proportion of (former) PWID was higher (35% versus 12%, p<0.001). Four percent of the patients untreated for HCV never received cART, compared to 1% in the group treated for HCV (p<0.001).

Region of origin was significantly different between the two groups (overall p<0.001), with a higher proportion of patients from the Netherlands among the treated patients (69% versus 55%) and a lower proportion of patients from the Caribbean and Latin America (6% versus 11%). Also HCV genotype was significantly different between the two groups (overall p<0.001), with a higher proportion of genotype 1 (62% versus 51%) and a lower proportion of genotype 3 (8% versus 14%) among the treated patients compared to the untreated patients (51% and 14%). Presence of severe liver fibrosis (≥ Metavir score F3) was not significantly different between these two groups.

Characteristics of patients who failed treatment

Overall 68 patients failed treatment, of whom 14 failed DAAs and 54 patients failed a pegylated interferon-alpha based regimen. Compared to the patients who achieved SVR (n=1124), the proportion of (former) PWID was higher in the patients who failed treatment (21% versus 11%, p=0.02), and the proportion of MSM was lower (59% versus 75%, p=0.003). Furthermore, 3% of the patients who failed HCV treatment never received cART, compared to 1% in the group who achieved SVR (p=0.02). Other variables did not differ significantly between the two groups.

Of the patients who failed DAAs (n=14), 9 were MSM, 2 were (former) PWID and 3 had another HIV transmission route. Seven patients were infected with genotype 1a, 5 patients with genotype 4 and 2 patients with another HCV genotype. Three patients had severe liver fibrosis (≥ Metavir score F3).

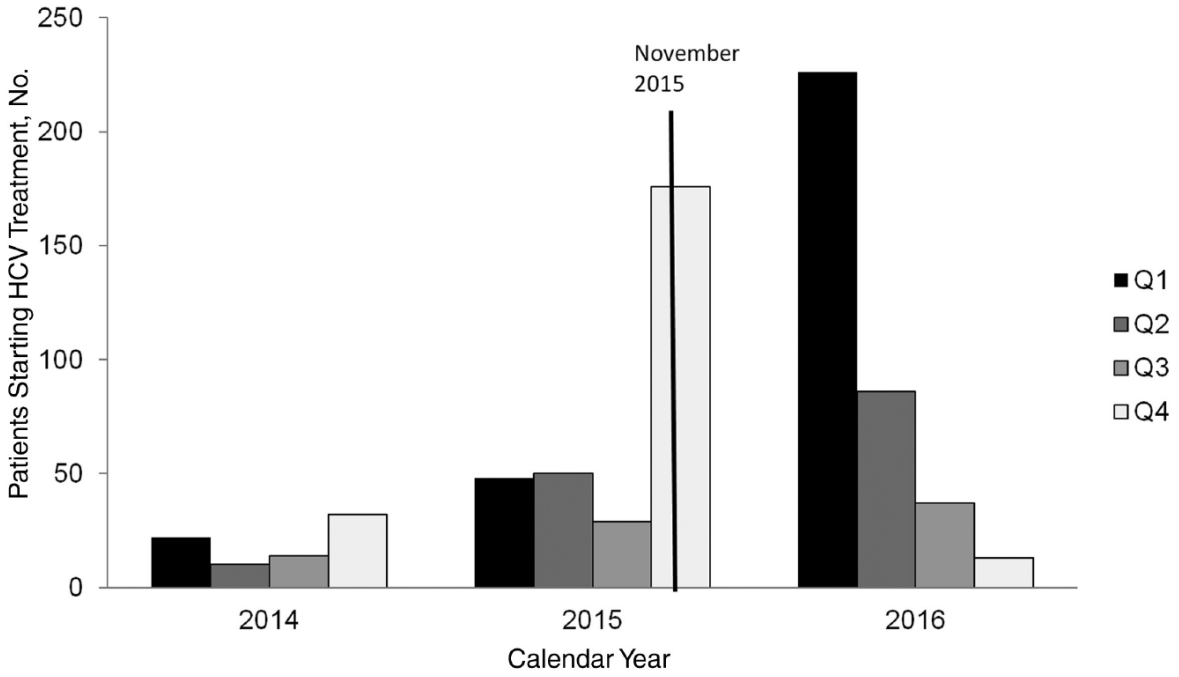


Figure 4 HCV treatment uptake per quarter in the years 2014, 2015 and 2016

Discussion

As of February 1st 2017 and only 15 months after DAAs were made available to all patients with chronic HCV in the Netherlands, 76% of the Dutch HIV/HCV-coinfected patients in care had been successfully treated for HCV. Another 6% are still undergoing DAA treatment or have completed treatment but are awaiting SVR12. The majority of this 6% can be expected to also be cured, as real-world SVR rates after DAA treatment in HIV/HCV-coinfected patients are well above 90%[5-8]. Our results demonstrate that in resource-unconstrained settings, a very high treatment uptake is possible in HIV/HCV-coinfected patients within only 15 months after unrestricted availability of DAAs. Treatment uptake and HCV cure rates were highest in MSM and significantly higher than in other categories of coinfected patients. Only 112 HIV/HCV-coinfected MSM remain to be treated. In the Netherlands, in contrast to other countries, ongoing HCV transmission occurs mainly among HIV-infected MSM[9] and transmission among PWID is nearly nonexistent as a result of successful harm reduction policies[10]. Therefore, it is promising that treatment uptake is highest among MSM which may favorably contribute to reduce ongoing HCV transmission in the Netherlands. However, the fact that treatment uptake in HIV/HCV-coinfected PWID in care was significantly lower when compared to the overall population of HIV/HCV-coinfected patients is an important signal that might reflect social, medical, psychiatric and/or substance-use associated factors or perceived barriers by practitioners as reviewed extensively by Grebely et al.[11].

Our study has several strengths. The data we analyzed were derived from the longstanding ATHENA cohort of HIV-infected patients that also includes data on HCV status and treatment. This cohort is representative of all HIV-infected patients in the Netherlands, as it captures data from over 98% of all HIV-infected patients in care. Additionally, for this study an extra query was performed by contacting each HIV treatment center with a list of HCV co-infected patients whose treatment status remained uncertain or whose SVR12 results were pending in February 2017. As a result of this query we have made the data of this study as up-to-date as possible. To our best knowledge, this is the first study that provides truly nationwide data on HCV treatment uptake and cure rates after unrestricted DAA

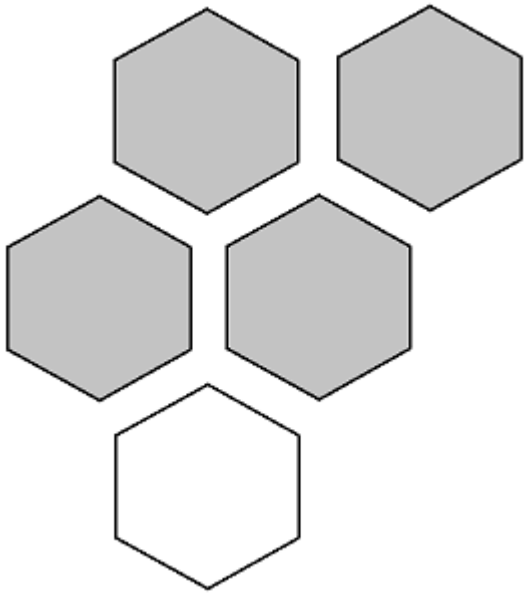
availability for chronic hepatitis C in HIV/HCV-coinfected patients. If this rapid treatment scale up is continued, it may contribute to the future elimination of HCV among HIV/HCV-coinfected patients in the Netherlands. Of note however, additional harm reduction strategies and scaling up of HCV testing are likely to be necessary to eventually reach elimination[2,3]. Our study has some limitations. First, only the patients who were retained in care could be analyzed and therefore we were unable to provide data on the 114 patients who were lost to follow-up. However, these 114 patients represent only 6% (114/1989) of the HIV/HCV-coinfected patients overall. Collaboration between different stakeholders could possibly lead to (re-)identification of these patients and further elimination of HCV from the HIV/HCV-coinfected population. Second, a certain proportion of HCV infections in this population will remain undiagnosed as alanine aminotransferase (ALT) levels may occasionally remain within normal limits after HCV infection[12]. However, 99% of HIV-infected patients currently in care in the Netherlands have been tested for HCV at least once[4]. Third, only the most recent treatment and its outcome was included in the cascade. This is an appropriate method to visualize the overall treatment uptake, but in the calculation of the SVR rate it may have led to an overestimation, as for patients who failed a first treatment with DAAs and were successfully treated a second time, only the second result was taken into account in the calculation. Real-world SVR rates found in other studies in HIV/HCV-coinfected patients are indeed lower than the 98% that we report[5-8]. Furthermore, due to the cross-sectional design of our analysis HCV reinfections after DAA treatment could not be taken into account. As HCV reinfections are common in HIV-infected MSM[13,14], a certain proportion of the population will become reinfected with HCV and therefore be again in need of effective treatment.

Although treatment uptake and HCV cure rates are high, the group of patients that remains to be treated will be the most challenging. To target this remaining subgroup of HIV/HCV-coinfected patients, we provided each HIV treatment center with a coded list of patients who according to the information available in ATHENA remain in need of curative treatment, in order to facilitate the identification and re-evaluation of these patients.

In conclusion, we demonstrate a very high treatment uptake among HIV/HCV-coinfected patients. Fifteen months after unrestricted availability of DAAs, overall 76% of Dutch HIV/HCV-coinfected patients have been cured for HCV and an additional 6% are either still being treated with DAAs or awaiting their treatment result.

References

1. Arends JE, Kracht PA, Hoepelman AI, European Study Group for Viral Hepatitis. Performance of hepatitis C virus (HCV) direct-acting antivirals in clinical trials and daily practice. Clin Microbiol Infect 2016;22:846-52.
2. Salazar-Vizcaya L, Kouyos RD, Zahnd C, et al. Hepatitis C virus transmission among human immunodeficiency virus-infected men who have sex with men: Modeling the effect of behavioral and treatment interventions. Hepatology 2016;64:1856-69.
3. Martin NK, Thornton A, Hickman M, et al. Can Hepatitis C Virus (HCV) Direct-Acting Antiviral Treatment as Prevention Reverse the HCV Epidemic Among Men Who Have Sex With Men in the United Kingdom? Epidemiological and Modeling Insights. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2016;62:1072-80.
4. van Sighem AI, Boender TS, Wit FWNM, Smit C, Matser A, Reiss P. Monitoring Report 2016. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Stichting HIV Monitoring;Available at: www.hiv-monitoring.nl. Accessed 14 July 2017.
5. Ingiliz P, Christensen S, Kimhofer T, et al. Sofosbuvir and Ledipasvir for 8 Weeks for the Treatment of Chronic Hepatitis C Virus (HCV) Infection in HCV-Monoinfected and HIV-HCV-Coinfected Individuals: Results From the German Hepatitis C Cohort (GECCO-01). Clin Infect Dis 2016;63:1320-4.
6. Piroth L, Wittkop L, Lacombe K, et al. Efficacy and safety of direct-acting antiviral regimens in HIV/HCV-co-infected patients - French ANRS CO13 HEPAVIH cohort. Journal of hepatology 2017.
7. Menard A, Colson P, Catherine D, et al. First Real Life Evidence of New Direct-acting Antivirals (DAA) in Co-infected HIV HCV Patients: Better than Ever. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2016;62:947-9.
8. Milazzo L, Lai A, Calvi E, et al. Direct-acting antivirals in hepatitis C virus (HCV)-infected and HCV/HIV-coinfected patients: real-life safety and efficacy. HIV medicine 2017;18:284-91.
9. Vanhommerig JW, Stolte IG, Lambers FA, et al. Stabilizing incidence of hepatitis C virus infection among men who have sex with men in Amsterdam. J Acquir Immune Defic Syndr 2014;66:e111-5.
10. de Vos AS, van der Helm JJ, Matser A, Prins M, Kretzschmar ME. Decline in incidence of HIV and hepatitis C virus infection among injecting drug users in Amsterdam; evidence for harm reduction? Addiction 2013;108:1070-81.
11. Grebely J, Oser M, Taylor LE, Dore GJ. Breaking down the barriers to hepatitis C virus (HCV) treatment among individuals with HCV/HIV coinfection: action required at the system, provider, and patient levels. J Infect Dis 2013;207 Suppl 1:S19-25.
12. Vanhommerig JW, Schinkel J, van der Valk M. Seven years of chronic hepatitis C virus infection in an HIV-infected man without detectable antibodies. Aids 2015;29:389-90.
13. Lambers FA, Prins M, Thomas X, et al. Alarming incidence of hepatitis C virus re-infection after treatment of sexually acquired acute hepatitis C virus infection in HIV-infected MSM. Aids 2011;25:F21-7.
14. Ingiliz P, Martin TC, Rodger A, et al. HCV reinfection incidence and spontaneous clearance rates in HIV-positive men who have sex with men in Western Europe. Journal of hepatology 2017;66:282-7.



Chapter 5

Declining HCV incidence in Dutch HIV-positive men who have sex with men after unrestricted access to HCV therapy

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Clinical Infectious Diseases, 2018

Abstract

Background

Direct acting antivirals (DAA) cure 95% of patients infected with hepatitis C (HCV). Modeling studies predict that universal HCV treatment will lead to a decrease in the incidence of new infections but real-life data are lacking. The incidence of HCV among Dutch HIV-positive men who have sex with men (MSM) has been high for >10 years. In 2015 DAA became available to all Dutch HCV patients and resulted in a rapid treatment uptake in HIV-positive MSM. We assessed whether this uptake was followed by a decrease in the incidence of HCV infections in HIV-positive MSM.

Methods

Two prospective acute HCV treatment studies enrolled patients in 17 Dutch HIV centers, having 76% of the total HIV-positive MSM population in care in the Netherlands. Patients were recruited in 2014 and 2016, the years preceding and following unrestricted DAA availability. We compared the HCV incidence in both years.

Results

The acute HCV incidence decreased from 93 infections during 8290 person years of follow up in 2014 (11.2/1000 PYFU, 95% CI 9.1-13.7) to 49 during 8961 PYFU in 2016 (5.5/1000, 95% CI 4.1–7.2). The incidence rate ratio of 2016 compared with 2014 was 0.49 (95% C.I. 0.35-0.69). Simultaneously, a significant increase in the percentage positive syphilis (+2.2%) and gonorrhea (+2.8%) tests in HIV-positive MSM was observed at sexual health clinics across the Netherlands and contradicts a decrease in risk behavior as an alternative explanation.

Conclusions

Unrestricted DAA availability in the Netherlands was followed by a 51% decrease in acute HCV infections among HIV-positive MSM.

Background

A high incidence of acute hepatitis C (HCV) infections in HIV-positive men who have sex with men (MSM) has been observed in many European countries as well as in Australia and the United States[1-3]. Indeed, during anal intercourse and additional high risk behavior with increased likelihood of blood-blood contact, HCV can be readily transmitted from man to man[4]. This contrasts with the very low incidence of transmission during heterosexual contacts[5]. Several recent studies described an acute HCV *incidence* in Dutch HIV-positive MSM of 1.1% or 11/1000 person years of follow up (PYFU)[6-8]. This is an extremely high incidence in a country where the overall HCV *prevalence* is estimated at 0.2%.[9] Van Santen et al. described a comparably high incidence of acute HCV among HIV-positive MSM in several other European countries[10].

As of July 2014, interferon free HCV therapy with direct acting antivirals (DAA) became reimbursed for all Dutch inhabitants with chronic HCV induced severe liver fibrosis or cirrhosis. At that time, the very high costs of these drugs were the reason why DAA therapy did not became available to all patients infected with HCV. Eventually, the restriction to patients with severe liver disease was lifted on November the 1st 2015. As a result, the Netherlands was one of the first European countries in which DAA therapy became available to all chronically HCV infected patients without any restrictions.

We recently showed that the unrestricted DAA availability was followed by a very rapid HCV treatment uptake among HIV-positive MSM with chronic HCV. Indeed, already 76% of the Dutch HIV-positive MSM ever infected with HCV were shown to be cured of their HCV infection as of January 2017[11]. Mathematical modeling studies have predicted that by decreasing the pool of infectious persons in the population, the immediate treatment with DAA of all HCV infected HIV-positive MSM would lead to a progressive decline in the incidence of acute HCV infections[12-14]. However, this assumed decline in incidence has yet to be confirmed with real life observational data.

Therefore, the aim of this study was to investigate whether the countrywide rollout of DAA was followed by a decline in the number of acute HCV infections among HIV-positive MSM within the Netherlands.

Patients and methods

According to Dutch HIV treatment guidelines, HCV infections in HIV-positive MSM attending the HIV outpatient clinic are diagnosed by HCV antibody testing (followed by HCV RNA testing when antibodies are positive) at entry into HIV care. Thereafter, HCV IgG testing is performed once a year and, HCV RNA testing is also done if a new alanine aminotransferase (ALT) elevation is observed. Liver enzymes are measured during the biannual HIV viral load monitoring.

An acute HCV infection was defined as a positive HCV RNA test, preceded by a negative HCV test in the previous 12 months. Because HIV centers in the Netherlands store leftover plasma from each outpatient visit, retesting of superfluous plasma from the preceding outpatient visit was possible in the majority of the patients to confirm that the patient had been HCV-negative in the previous year. However, if stored plasma was not available, a new HCV diagnosis was also considered to be an acute HCV infection if a normal ALT measurement within the last 12 months preceded the first positive HCV-RNA test and a documented negative HCV test was available from any time in the past and no other possible explanation for the ALT elevation was found[15].

An acute HCV *re*-infection was defined as a positive HCV RNA test after a previously documented sustained virological response 12 weeks or more after the end of HCV therapy. For patients treated in the Dutch Acute HCV in HIV Studies (DAHHS), in case HCV RNA became detectable again within 12 weeks after the end of therapy, HCV RNA was also genotyped and sequenced to differentiate relapse from reinfection.

Currently there is no systematic registry in place for acute HCV infections in the Netherlands. We therefore used the data from two prospective studies as a proxy. The DAHHS-group is a network of 17 hospitals that performs multicenter clinical trials on the

treatment of AHCV[16,17]. None of the currently available DAA have been registered for the treatment of an acute HCV infection. Therefore and to evaluate the effectivity of DAA for the treatment of acute HCV, the DAHHS1 and 2 studies were designed. Both are prospective studies that evaluated (DAHHS1 in 2014) or are evaluating (DAHHS2 in 2016 and ongoing) different DAA-based options for the treatment of acute HCV infection. Because these studies enroll(ed) patients prospectively they enabled us to register all acute HCV infections diagnosed in the DAHHS centers and compare the incidence of acute HCV infections among HIV-positive MSM in the year preceding (2014) and in the first year after (2016) interferon free DAA became available for the treatment of chronic HCV in the Netherlands.

Patient characteristics were collected by the treating physician and transferred to the study coordinator after pseudonymization. All patients consented to have their data used for research purposes in the context of the HIV ATHENA cohort[18]. Data on the number of HIV-positive MSM and on the HCV prevalence among HIV-positive MSM in care across all HIV centers in the Netherlands were provided by Stichting HIV Monitoring (SHM, HIV Monitoring Foundation), responsible for data collection of the patients in the ATHENA cohort. The ATHENA cohort consists of 98% of the patients diagnosed with and in care for HIV in the Netherlands[18].

The incidence of acute HCV in the year 2014, the last year before DAA became available and 2016, the first year after unrestricted DAA availability was calculated by dividing the number of acute HCV cases by the PYFU of all HIV-positive MSM in that year in the 17 study centers. To compare the acute HCV incidence in 2016 with 2014, we calculated the incidence rate ratio (IRR) with 95% confidence intervals.

Because HCV infections are transmitted sexually among MSM, national data on the incidence of the sexually transmitted diseases (STDs) syphilis and gonorrhea in MSM were used as a surrogate marker for the evaluation of possible trends in sexual risk behavior. These data are provided by the STD/HIV Surveillance Unit of the National Institute for Public Health and Environment (RIVM). The RIVM collects, integrates and interprets data from multiple surveillance sources in the Netherlands, including data from registration by sentinel STD clinics and HIV treatment centers[19,20].

Results

In 2014, 93 acute HCV infections were diagnosed in the 17 study centers during 8290 PYFU (incidence of 11.2/1000 PYFU, 95% CI 9.1-13.7). In contrast, 49 acute HCV infections were diagnosed during 8961 PYFU in 2016 (incidence of 5.5/1000 PYFU, 95% CI 4.1–7.2). Thus, the incidence rate ratio of 2016 compared with 2014 was 0.49 (95% C.I. 0.35 - 0.69). During the first 4 months of 2017, the incidence was 5.6 per 1000 PYFU (17/3047 PYFU) and comparable to the overall incidence in 2016. In 2014, the majority of acute HCV infections was caused by HCV genotype 1 (72/93; 77%). The proportion of genotype 1 in acute HCV infection decreased in 2016 (27/49; 55%) (figure 1). Consequently, the incidence rate ratio for genotype 1 infections comparing 2016 to 2014 was 0.35 (95% CI 0.22-0.54). Looking at the smaller group of genotype 4 infections only, the decline was less pronounced and not statistically significant (IRR 0.77; 95% CI 0.54-1.09). A change in the distribution of the nation of origin of the patients diagnosed with an acute HCV of the genotype 1 or 4 could not explain the difference in decline in the incidence of genotype 1 and 4. Indeed, 23/93 patients with an acute HCV diagnosed in 2014 were born outside the Netherlands which was comparable to 2016 (8/49, p=0.29). Figure 2 illustrates the incidence of acute HCV for every 4 months of the calendar year and per genotype in 2014, 2016 and the first 4 months of 2017.

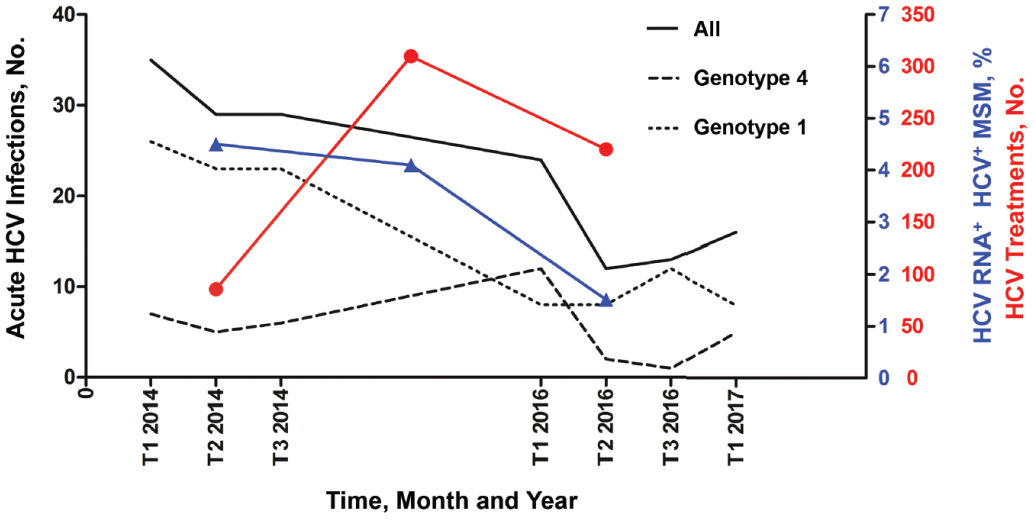


Figure 2 Left axis Acute HCV infections per 4 months and per genotype **Right axis** Percentage HCV RNA positive HIV-positive MSM (**blue**) and number of HCV treatments (**red**) in the Netherlands per year (both personal communication SHM).

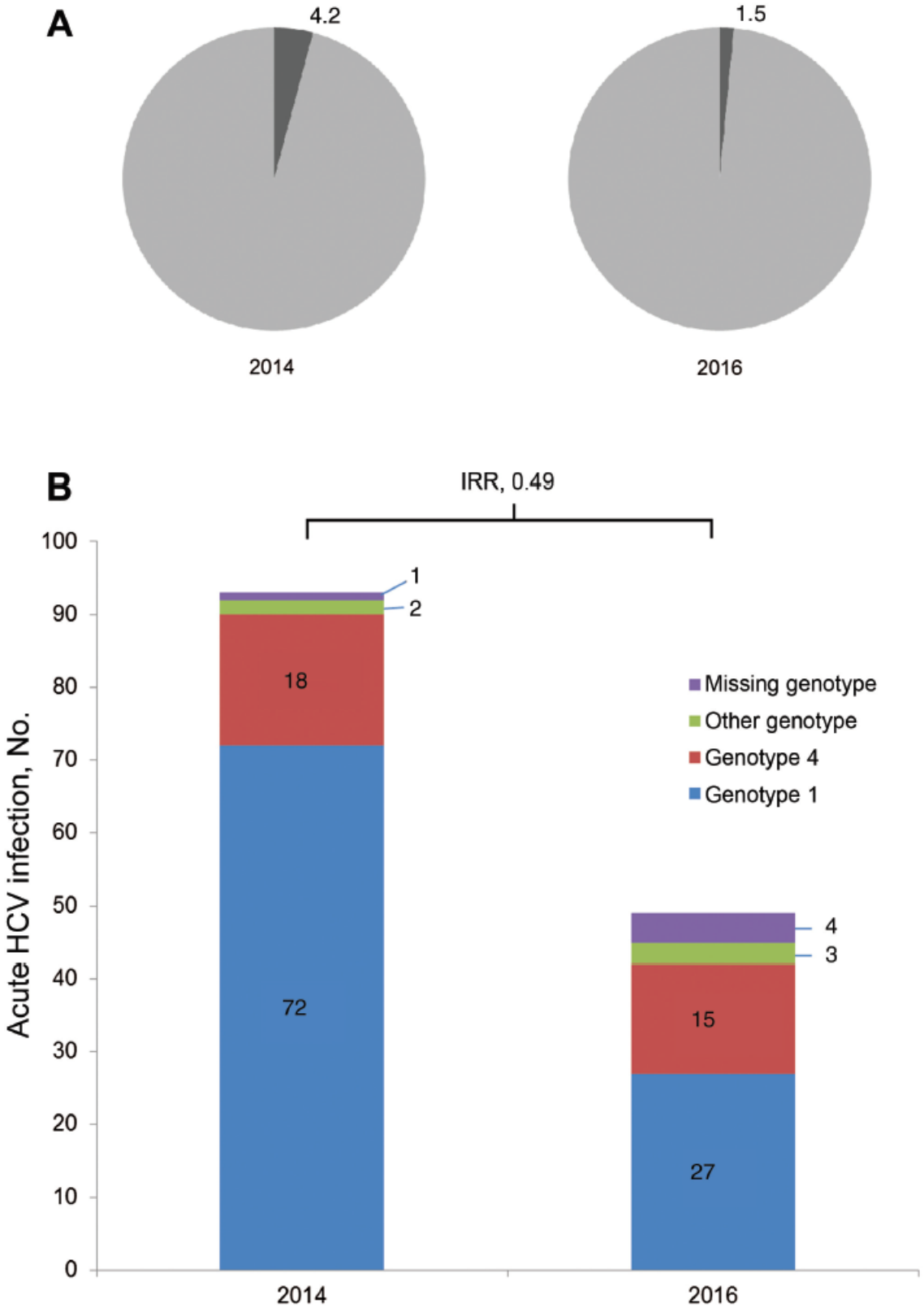


Figure 1 HCV infections in HIV-positive MSM in care in the Netherlands

A *Percentage of HIV-positive MSM in the Netherlands that remained HCV RNA positive in 2014 and 2016*

B *Acute HCV infections in 2014 and 2016*

Table 1 Baseline characteristics of patients with an acute hepatitis C infection in 2014 and 2016

	2014	**2016**	**p-value**
Acute HCV[a] infections	n=93	n=49	
Age in years (mean +- SD)	42 (± 9)	46 (± 9)	0.06
On cART[b] (%)	84 (90)	43 (94)	0.53
CD4 cells/mm^3 (median, IQR)	610 (430-810)	620 (465-763)	0.86
Reinfection (%)	21 (23)	12 (25)	0.75
HCV genotype (%)			0.02
genotype 1	72 (77)	27 (55)	
genotype 2	2 (2)	1 (2)	
genotype 3	0	2 (4)	
genotype 4	18 (19)	15 (31)	
Missing	1 (1)	4 (8)	
HCV genotype 1			0.57
subtype a	68	27	
subtype b	4	0	

The absolute number of acute HCV infections decreased both in patients with a first acute HCV infection and in patients that had an acute HCV reinfection after a previously cured HCV infection, while the proportion of reinfections remained constant between 2014 and 2016 (23% (21 of 93) and 24% (12 of 49), respectively) (p=0.8) (table 1).

In the years that preceded the introduction of DAA, the proportion of HIV-positive MSM in the Netherlands who were HCV RNA positive (and thus a potential source for new infections) was stable at 4,2 % in 2013 (396/9513) and 4,1% in 2015 (450/11070). The unrestricted access to DAA caused a prompt and substantial decrease of this infectious pool to 1.5% (176/11749) by the end of 2016 (data provided by SHM; figure 1). When comparing 2016 to 2014, a substantial increase in the percentage of positive syphilis (from 6.6% to 8.4%; resp. 281/4240 and 435/5185; p=0.001) and gonorrhea tests (from 16.4% to 19.2%; resp. 697/4239 and 1005/5228; p<0.001) among HIV-positive MSM attending sentinel STD clinics in the Netherlands was observed[19,20].

Discussion

We observed a 51% decrease in acute HCV infections in 2016 compared to 2014. As far as we know, this is the first study that uses real-life data that lends support to what recent modeling studies have predicted; universal HCV therapy of all HIV-positive MSM chronically infected with HCV will result in a decrease in the number of acute HCV infections in this population[12-14].

The decline of acute HCV infections was more pronounced for HCV genotype 1 (65% decrease) than for genotype 4 (23%). Possibly treatment of acute HCV infection in the context of the DAHHS1 study (only HCV genotype 1 infections could be treated in this study) may explain the more substantial decrease of genotype 1 than 4 infections that we observed. Indeed, as much as 79% of the 72 patients diagnosed with an acute HCV genotype 1 infection in 2014 in the 17 study centers were treated in the DAHHS1 study and 86% of them were cured and therefore no longer a source of new genotype 1 infections[15,16]. However, the chronic HCV treatment uptake among Dutch HIV-positive patients in general did not differ between genotype 1 and 4 and neither was there a difference in uptake in relation to the country of origin of these patients, so a disparity in HCV treatment uptake based on country of origin or genotype cannot explain the smaller decrease in incidence of acute HCV of the genotype 4 compared with genotype 1. It is well known that acute HCV outbreaks occur frequently and this may have been the case for genotype 4. Indeed, as illustrated in figure 2, 80% of the genotype 4 infections in 2016 were diagnosed in the first 4 months of 2016.

The incidence of HCV reinfection among HIV positive MSM that were cured of a previous HCV infection has historically been very high[21]. Therefore, this subgroup of patients may be at the core of the HCV epidemic. To this regard, it is reassuring that we observed a decrease in the number of HCV reinfections as well (from 21 to 12), despite a substantial increase in the population at risk for reinfection. Indeed, as a result of the HCV treatment uptake and the consequent decline of HCV RNA positive patients from 4.2% in 2013 to 1.5% at the end of 2016, the number of patients that were cured of HCV and therefore become at risk for a reinfection has increased substantially.

In contrast to the decline in acute HCV infections, the number of MSM diagnosed with syphilis or gonorrhea at STD clinics across the Netherlands increased substantially in 2016. Therefore, it is very unlikely that the decline in acute HCV infections that we observed is the result of reduced sexual risk behavior.

In 2015, Vanhommerig et al. found that in HIV-positive MSM, receptive unprotected anal intercourse, sharing sex toys, unprotected fisting and a recent diagnosis of ulcerative STDs were all independent risk factors for the acquisition of acute HCV infection[4]. Also, intravenous drug use (IVDU) before or during sex (also called slamming or slamsex) was another significant risk factor. However, only 11% (9 of 82) of the patient with an acute HCV infection included in their study reported IVDU as a risk factor. Therefore, we consider it unlikely that a decrease in IVDU among HIV-positive MSM in 2016 compared with 2014 can explain our observations. Second, a recent study into Q80K phylogeny in Dutch HCV genotype 1a infected patients showed no intermingling of HIV-positive MSM and PWID[22]. Although injection drug use (whether IV or subcutaneously) during sex does occur in a small number of HIV-positive MSM[4] and sexual networks seem to be highly dynamic[23], it is unlikely that HCV strains from Dutch PWID fuel the HCV epidemic in Dutch HIV-positive MSM[22].

The strength of our study is the prospective data collection on acute HCV incidence in 17 HIV centers. These 17 centers are representative for the whole of the Netherlands as they are located in all major Dutch cities and provide HIV therapy to more than 75% of all HIV-positive MSM in care in the Netherlands.

Our study has several limitations. First, an observational study cannot prove that the DAA uptake is the cause of the decline in acute HCV incidence. A substantial change in risk behavior may have led to a similar decrease. We did not measure IVDU in our cohort, however, as stated above, IVDU does not appear to be an important risk behavior in Dutch HIV positive MSM although this may change over time. Second, from modeling studies in PWID it is known that treatment scale up can have a bigger impact on a stable versus an increasing HCV epidemic[24]. In contrast to the stable HCV incidence in HIV-positive MSM in the Netherlands, other parts of Europe still see a rising incidence of HCV infections[10], thus treatment scale up might not have the same effect on those epidemics. Therefore, the

extrapolation of our data to other settings should be done with caution. Third, the proportion of chronically HCV infected patients, whom are very unlikely to be diagnosed with a new acute HCV superinfection (as they are already HCV RNA positive) was not subtracted from the total PYFU of HIV-positive MSM in the incidence calculations. However, excluding them from the IRR calculation would further lower the IRR from 0.49 to 0.47. Fourth, by the end of 2015 a certain number of MSM were living with HIV but where unaware of their HIV infection and therefore not in care. As such, our conclusions cannot be extrapolated to this HIV infected MSM population. However, in the Netherlands this fraction has been estimated to be small at around 10%[25]. Finally, acute HCV infections often occur in localized outbreaks and therefore, temporary fluctuations in the incidence can be expected. Therefore, longer-term data are needed to confirm that the decrease we have observed is not the result of an extreme fluctuation by chance.

Although the 51% decrease of acute HCV infections we describe is encouraging, it is very unlikely that DAA therapy for all HCV co-infected patients with HIV as a single intervention will lead to elimination of HCV among Dutch HIV-positive MSM[12,13]. Although preliminary, this is also suggested by the apparent lack of a further decline in incidence during the first 4 months of 2017. Other interventions are thus needed.

First, the incidence of acute HCV infections in HIV-positive MSM is high in major cities of all neighboring countries of the Netherlands[26,27]. Due to the continuous restrictions of DAA to patients with severe liver disease in some of the neighboring countries, the DAA treatment uptake in these countries has been limited. Therefore, cross-border HCV transmissions will continue to occur as long as a comparable treatment uptake does not occur in neighboring countries[28].

Second, while in the Netherlands the prevalence of HCV infection in HIV-negative MSM attending STD clinics[7] and the number of reported cases of acute HCV infection in HIV-negative MSM has been low[29], the prevalence is probably substantially higher in a certain subset of MSM. Exemplary for this are the very recent observations in an HIV pre-exposure prophylaxis (PrEP) implementation project in Amsterdam. Upon entering the PrEP program 15 patients (4%) had detectable HCV RNA[30]. Also, risk compensation and an increase in the incidence of STD during PrEP use may occur and could lead to an increase in HCV

transmission among PrEP users[31]. Therefore, we think that monitoring of the prevalence of HCV among HIV-negative MSM engaging in unprotected anal intercourse and in particular MSM using PrEP is needed.

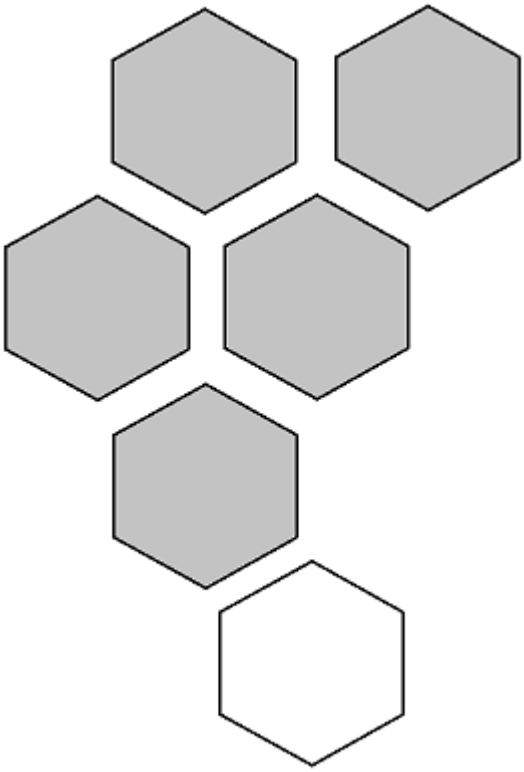
Third, several studies have observed an extremely high acute HCV reinfection rate in patients cured of a previous HCV infection[26,32,33]. Therefore, a specific focus on HIV-positive MSM with a history of a HCV infection is needed. This may consist of very frequent (e.g. every 3 months) HCV testing with the aim of diagnosing and treating HCV re-infections as early as possible[34]. Last, but not least, counseling on sexual risk behavior is important and when appropriate, referral to specialized clinics for problematic recreational drug use in the context of chemsex or slamsex is needed[13] as not only IVDU but also orally administrated drugs seem to be associated with HCV transmission among HIV-positive MSM[4].

In conclusion, a 51% decrease of acute HCV infections in HIV-positive MSM was observed in 2016 compared to 2014. A HCV “treatment as prevention” effect that was caused by the rapid DAA treatment uptake among HIV-positive MSM with chronic HCV is the most plausible explanation for this decline.

References

1. Wandeler G, Gsponer T, Bregenzer A, et al. Hepatitis C virus infections in the Swiss HIV Cohort Study: a rapidly evolving epidemic. Clin Infect Dis 2012;55:1408-16.
2. Hagan H, Jordan AE, Neurer J, Cleland CM. Incidence of sexually transmitted hepatitis C virus infection in HIV-positive men who have sex with men. Aids 2015;29:2335-45.
3. Ghisla V, Scherrer AU, Nicca D, Braun DL, Fehr JS. Incidence of hepatitis C in HIV positive and negative men who have sex with men 2000-2016: a systematic review and meta-analysis. Infection 2016.
4. Vanhommerig JW, Lambers FA, Schinkel J, et al. Risk Factors for Sexual Transmission of Hepatitis C Virus Among Human Immunodeficiency Virus-Infected Men Who Have Sex With Men: A Case-Control Study. Open Forum Infect Dis 2015;2:ofv115.
5. Terrault NA DJ, Murphy EL, Tavis JE, Kiss A, Levin TR, Gish RG, Busch MP, Reingold AL, Alter MJ. Sexual transmission of hepatitis C virus among monogamous heterosexual couples: the HCV partners study. Hepatology 2013;Mar;57(3):881-9.
6. van de Laar TJ, Matthews GV, Prins M, Danta M. Acute hepatitis C in HIV-infected men who have sex with men: an emerging sexually transmitted infection. Aids 2010;24:1799-812.
7. Urbanus AT, Van De Laar TJ, Geskus R, et al. Trends in hepatitis C virus infections among MSM attending a sexually transmitted infection clinic; 1995-2010. Aids 2014;28:781-90.
8. Vanhommerig JW, Stolte IG, Lambers FA, et al. Stabilizing incidence of hepatitis C virus infection among men who have sex with men in Amsterdam. J Acquir Immune Defic Syndr 2014;66:e111-5.
9. Vriend HJ VVM, Prins M, Urbanus AT, Boot HJ, Op De Coul EL. Hepatitis C virus prevalence in The Netherlands: migrants account for most infections. Epidemiol Infect 2013;Jun;141(6):1310-7.
10. Van Santen DK, Van Der Helm JJ, Del Amo J, et al. Lack of decline in Hepatitis C Virus incidence among HIV-positive men who have sex with men during 1990-2014. J Hepatol 2017.
11. Boerekamps A, Newsum A, Smit C, Reiss P, Richter C, van der Valk M, Arends J, Brinkman K, Rijnders B, the hepatitis working group SHM. Unrestricted DAA access in the Netherlands: rapid therapy uptake in HIV/HCV+ patients. Oral presentation at CROI conference February 13–16, 2017 Seattle, Washington, abstract 136.
12. Hullegie SJ NB, Rijnders BJ, de Knegt RJ, Rockstroh JK, Boucher CA, van de Vijver DA. Is HCV Elimination Possible? A Modeling Study of HIV-Positive MSM. Oral presentation at CROI conference February 22–25, 2016 Boston, Massachusetts, abstract 536.
13. Salazar-Vizcaya L, Kouyos RD, Zahnd C, et al. Hepatitis C virus transmission among human immunodeficiency virus-infected men who have sex with men: Modeling the effect of behavioral and treatment interventions. Hepatology 2016;64:1856-69.
14. Martin NK, Thornton A, Hickman M, et al. Can Hepatitis C Virus (HCV) Direct-Acting Antiviral Treatment as Prevention Reverse the HCV Epidemic Among Men Who Have Sex With Men in the United Kingdom? Epidemiological and Modeling Insights. Clin Infect Dis 2016;62:1072-80.
15. Arends JE, Lambers FA, van der Meer JT, et al. Treatment of acute hepatitis C virus infection in HIV+ patients: Dutch recommendations for management. Neth J Med 2011;69:43-9.
16. Hullegie SJ CM, van den Berk GE, van der Meer JT, Posthouwer D, Lauw FN, Leyten EM, Koopmans PP, Richter C, van Eeden A, Bierman WF, Newsum AM, Arends JE, Rijnders BJ. Boceprevir, peginterferon and ribavirin for acute hepatitis C in HIV infected patients. J Hepatol 2016;Apr;64(4):807-12.
17. Dutch Acute HCV in HIV Study (DAHHS-2): Grazoprevir/Elbasvir for Acute HCV (DAHHS-2). NCT02600325.
18. van Sighem A.I. BTS, Wit F.W.N.M., Smit C., Matser A., Reiss P. Monitoring Report 2016. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Stichting HIV Monitoring 2016;Available online at www.hiv-monitoring.nl.
19. A.A.M. van Oeffelen FvA, I.V.F. van den Broek, E.L.M. Op de Coul, P.J. Woestenberg, J.C.M. Heijne, C. den Daas, S.H.I. Hofstraat, A.I. van Sighem, M.M.J. Nielen, B.H.B. van Benthem. Sexually transmitted infections including HIV, in the Netherlands in 2014. Rijksinstituut voor Volksgezondheid en Milieu RIVM;26-Jun-2015

20. Visser M vAF, van Oeffelen AAM, van den Broek IVF, Op de Coul ELM, Hofstraat SHI, Heijne JCM, den Daas C, Hoenderboom BM, van Wees DA, Basten M, Woestenberg PJ, Götz HM, van Sighem AI, de Hoon S, van Benthem BHB,. Sexually transmitted infections including HIV, in the Netherlands in 2016. Rijksinstituut voor Volksgezondheid en Milieu RIVM;23-Jun-2017
21. Midgard H, Weir A, Palmateer N, et al. HCV epidemiology in high-risk groups and the risk of reinfection. J Hepatol 2016;65:S33-45.
22. Newsum AM, Ho CK, Lieveld FI, et al. The hepatitis C virus nonstructural protein 3 Q80K polymorphism is frequently detected and transmitted among HIV-infected MSM in the Netherlands. Aids 2017;31:105-12.
23. Vanhommerig JW, Bezemer D, Molenkamp R, et al. Limited overlap between phylogenetic HIV and HCV clusters illustrates the dynamic sexual network structure of Dutch HIV-infected MSM. Aids 2017.
24. Fraser H, Zibbell J, Hoerger T, et al. Scaling up HCV prevention and treatment interventions in rural USA - model projections for tackling an increasing epidemic. Addiction 2017.
25. van Sighem A.I. BTS, Wit F.W.N.M., Smit C., Matser A., Reiss P. . Monitoring Report 2016. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Stichting HIV Monitoring, 2016, Available online at wwwhiv-monitoringnl.
26. Ingiliz P, Martin TC, Rodger A, et al. HCV reinfection incidence and spontaneous clearance rates in HIV-positive men who have sex with men in Western Europe. J Hepatol 2017;66:282-7.
27. Apers L, Koole O, Bottieau E, et al. Incidence of HCV and sexually transmitted diseases among hiv positive msm in antwerp, belgium, 2001-2011. Acta Clin Belg 2013;68:421-6.
28. van de Laar T, Pybus O, Bruisten S, et al. Evidence of a large, international network of HCV transmission in HIV-positive men who have sex with men. Gastroenterology 2009;136:1609-17.
29. Sexually transmitted infections in the Netherlands in 2015. National Institute for Public Health and the Environment;May 2016 www.rivm.nl/en.
30. Hoornenborg E, Achterbergh RCA, Schim Van Der Loeff MF, et al. Men who have sex with men starting pre-exposure prophylaxis (PrEP) are at risk of HCV infection: evidence from the Amsterdam PrEP study. Aids 2017.
31. MA Montano JD, LA Barbee, MR Golden, CM Khosropour. CHANGES IN SEXUAL BEHAVIOR AND STI DIAGNOSES AMONG MSM USING PREP IN SEATTLE, WA. CROI February 13-16, 2017 Seattle, Abstract Number: 979.
32. Lambers FA, Prins M, Thomas X, et al. Alarming incidence of hepatitis C virus re-infection after treatment of sexually acquired acute hepatitis C virus infection in HIV-infected MSM. AIDS 2011;25:F21-7.
33. Martin TC, Martin NK, Hickman M, et al. Hepatitis C virus reinfection incidence and treatment outcome among HIV-positive MSM. Aids 2013;27:2551-7.
34. S. Popping BEN, J.J.A. van Kampen, A. Verbon, C.A.B. Boucher, D.A.M.C. van de Vijver. Intensive hepatitis C monitoring in previously HCV infected HIV-positive MSM is a cost saving method to reduce the HCV epidemic. Oral at NCHIV 2016, abstract number O10, http://nchivorg/abstracts/ 2016.



Chapter 6

Case series on acute HCV in HIV-negative men in regular clinical practice: a call for action

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Research in context

What was known on this topic?

Sexually acquired acute hepatitis C infection used to be regarded as limited to HIV-positive men who have sex with men. Several large cohort studies showed a very low prevalence in HIV-negative men who have sex with men, comparable to the HCV prevalence in the general population.

What does this add?

With this case series we want to raise awareness among a broad range of Dutch clinicians. Sexually transmitted hepatitis C infection seems to be no longer limited to HIV-positive MSM, at least a subgroup of HIV-negative MSM are probably at increased risk.

With the advent of pre-exposure prophylaxis (PrEP; protects against HIV infection), clinicians should be aware of the possibility of acute HCV infections in HIV-negative MSM and at least surveillance should be in place to gain inside the prevalence and incidence among this risk group.

Abstract

Background

The evidence that HIV treatment as prevention (TaSP) and HIV pre-exposure prophylaxis (PrEP) reduces the risk of HIV transmission is overwhelming. But as PrEP and TaSP can lead to increased sexual mixing between HIV positive and negative MSM, sexually transmitted infections like HCV that were thought to be limited to HIV infected MSM could become more frequent in HIV uninfected MSM as well. The objective of this study was to describe a series of cases of sexually transmitted HCV infections in *HIV-uninfected* MSM in the Netherlands and Belgium.

Methods

Through the Dutch Acute HCV in HIV Study (a Dutch-Belgian prospective multicentre study on the treatment of acute HCV infection, NCT02600325) and the Be-PrEP-ared study (a PrEP project in Antwerp, EudraCT2015-000054-37) several acute HCV infections were detected in HIV-negative men.

Results

A newly acquired HCV infection was diagnosed in ten HIV-negative MSM. HCV was diagnosed at a sexually transmitted infection (STI) clinic (n=2), by their general practitioner (n=2), by their HIV physician (n=1) or at a PrEP clinic (n=5). Ten patients reported unprotected anal intercourse and four had a concomitant STI at the time of HCV diagnosis. Six patients reported using drugs during sex.

Conclusions

Our observation calls for a larger nationwide epidemiological study on the prevalence, incidence and risk factors of HCV infection in HIV-uninfected MSM. In the changing landscape of TasP and PrEP, reliable and up-to-date epidemiological data on HCV among HIV-uninfected MSM are needed and will help in developing evidence-based testing policies.

Introduction

The World Health Organization recently released targets for hepatitis B and hepatitis C (HCV) elimination by 2030. They are comprised of a 90% reduction in new infections and a 65% reduction in hepatitis-related mortality by 2030[1]. One of the key populations at risk for HCV infection are HIV-infected men who have sex with men (MSM). Among HIV-infected individuals worldwide, it has been estimated that 2.4% are co-infected with HCV, yet this rises to 6.4% in HIV-infected MSM[2]. Because HIV-infected MSM in Western-Europe are in care for their HIV, treating all HIV-infected patients with an HCV co-infection for their HCV should be straightforward and HCV elimination in this specific subgroup might be possible[3,4]. Previous epidemiological data suggested that transmission of HCV among MSM was largely limited to HIV-infected MSM[5-7].

The evidence that HIV treatment as prevention (TaSP) and HIV pre-exposure prophylaxis (PrEP) reduces the risk of HIV transmission is overwhelming[8-11]. Although currently only four European countries have made PrEP available free of charge, generic tenofovir-disoproxil fumarate and emtricitabine in a single combination tablet are becoming available in certain European countries soon[12]. In Germany as well as the Netherlands negotiations have resulted in a substantial price reduction and will make PrEP affordable for many MSM.

Without any doubt, PrEP and TaSP will prevent many new HIV infections in MSM. However, it can be expected that PrEP and TaSP will also lead to increased sexual mixing between HIV positive and negative MSM. As such, sexually transmitted infections (STI's) like HCV that were thought to be limited to HIV infected MSM are likely to become more frequent in HIV uninfected MSM as well. A recent modelling study seems to confirm this and showed that sexual behaviour patterns are likely to drive the HCV infection pattern among HIV-positive MSM. If changes in these patterns occur, they could lead to HCV dissemination amongst HIV negative MSM and may decrease the impact of unrestricted HCV treatment for HIV-infected MSM on the HCV epidemic in MSM in general[13].

Very recently, Hoornenborg et al. showed that at the start of the Amsterdam PrEP study, the *prevalence* of HCV infection was 4% as 15 of the 375 MSM were *chronically* infected with HCV [14]. This illustrates that in a subgroup of HIV-uninfected MSM, the prevalence of HCV infection may be very substantial and this contrasts with what has been reported earlier about the HCV prevalence and incidence in HIV-negative MSM[6,15].

The objective of this study was to describe a series of cases and therefore create increased awareness about newly acquired HCV infections in *HIV-uninfected* MSM in the Netherlands and Belgium. All had tested HCV negative in the recent past.

Methods

Cases of HIV-negative MSM with a newly acquired HCV infection were collected in the context of an acute HCV treatment study (the Dutch-Belgian prospective multicentre study on the treatment of acute HCV infection (DAHHS-2, NCT02600325) or within an PrEP-project in Antwerp (Be-PrEP-ared; EudraCT2015-000054-37). Patients were initially diagnosed by their GP, their STI clinic, their HIV specialist or the PrEP project before they were referred to the DAHHS 2 study team.

All reported patients had been tested negative for HCV in the recent past. Patients were screened for HCV for different reasons in different settings as stated above and in table 1. HCV testing was done according to the local standard of care, which in all cases consisted of screening for HCV with HCV antibodies. Acute HCV was defined as a positive anti-HCV immunoglobulin G and a documented negative anti-HCV IgG in the previous 12 months (1). Patient characteristics and risk factors were retrieved from the patient files by the treating physician and transferred to the study coordinators after anonymization.

Both studies were approved by the institutional medical ethics committees. Enrolment in these studies was voluntary and a written informed consent was obtained in which the patients described in this report agreed that data and blood samples could be used for research purposes.

Results

From 1 January 2016 to July 2017 a total of ten HIV-negative MSM with a recently acquired HCV infection were reported (table 1). HCV infection was diagnosed at a sexually transmitted infection (STI) clinic (n=2), by the general practitioner (n=2), by their infectiologist (n=1) or at their PrEP clinic (n=5). All patients had a documented negative HCV test within the year preceding the HCV diagnosis. Of the patients diagnosed at the PrEP clinic, one was diagnosed before the start of PrEP and four after the start of PrEP. Median age was 39.5 years (range 25-59). HCV genotypes 1 was found in four patients, genotype 4 in two patients and was unknown in four patients. All patients reported unprotected anal intercourse (UAI), four had a concomitant STI at the time of HCV diagnosis and six reported drugs use during sex (chemsex). One patient reported intravenous drug use during sex (slamming). Clinical symptoms were non-specific or absent. Two patients were diagnosed after they had been informed of a HCV diagnosis in a partner.

Table 1 next page Characteristics of the 10 HIV-negative MSM with a newly acquired HCV infection

SS: slamsex, use of intravenous drugs during sex; UAI: unprotected anal intercourse. PN: partner notification; CS: chemsex, use of oral drugs during sex; PrEP: pre exposure prophylaxis for HIV; PEP: post exposure prophylaxis for HIV; STD: sexually transmitted disease; LGV: lymphogranuloma venereum; SVR12: sustained virological response 12 weeks after treatment; GP: general practitioner; AIN: anal intraepithelial neoplasia; $: DAHHS 2 study, NCT02600325; N/A: not applicable.

Risk factors	Geno-type	Symptomatic HCV infection?	Comorbidities at time of acute HCV infection	Earlier HCV infections	Year of acute HCV infection	Prior negative HCV test	HCV test indication	Tested at	Treatment given	SVR12
UAI CS SS	4	No	Chlamydia	No	2016	2014	PN	STI clinic Breda	Treated after HCV infection became chronic with sofosbuvir ledipasvir 8 weeks.	Yes
UAI	1a	No	Non	No	2016	2016	During PrEP study	PrEP clinic Amsterdam	Grazoprevir elbasvir 8 weeks.($)	Yes
UAI CS	Un-detec-table	Fatigue	LGV, syphilis, gonorrhoea, suspicion of AIN	No	2017	2016	LGV	STI clinic Rotterdam	No, spontaneous clearance.	N/A
UAI CS	4	Erythema multiforme	Gonorrhoea farynx, anal chlamydia	No	2016	2015	Routine testing	GP from region Leuven	Grazoprevir elbasvir 8 weeks.($)	Yes
UAI CS	1a	No	Non	No	2016	2016	Routine testing	GP from region West-Flanders	No, spontaneous clearance.	N/A
UAI	1a	No	Chlamydia, mycoplasma genitalium	No	2016	2016	During PrEP study	PrEP clinic Antwerp (patient from region Brussel)	Ongoing chronic infection.	N/A
UAI	Un-detec-table	Fatigue	Non	No	2016	2016	During PrEP study	PrEP clinic Antwerp, (patient from region Antwerp)	No, spontaneous clearance.	N/A
UAI CS	Un-detec-table	No	Depression, post-traumatic stress syndrome	No	2016	2015	During PrEP study	PrEP clinic Antwerp, (patient from region Antwerp)	No, spontaneous clearance.	N/A
UAI	Un-known	Proteinuria	Non	Un-known	2016	2016	Before start PrEP	PrEP clinic Antwerp, (patient from region East-Flanders)	Unknown.	N/A
UAI CS	1a	Fatigue	Non	No	2017	2017	PEP use	Hospital, Eindhoven	Grazoprevir elbasvir 8 weeks.($)	N/A

Discussion

Our case series shows that, even without an active screening policy, HCV infections are diagnosed in HIV-negative MSM as we were able to describe 10 cases of newly acquired HCV infections in Dutch and Belgian HIV-uninfected MSM. Other recent publications on HCV infections in HIV-negative MSM were the result of an active screening policy as part of an observational study or a PrEP program[14,16]. . Furthermore, very few studies on the epidemiology of HCV in HIV-uninfected MSM are available and none are collected in a way that incidence rates of acute HCV infection in HIV-negative MSM can be calculated to properly address the problem[6,7,14,16-18]. By design, case series cannot help to reliable estimate the size of the problem. We therefore call for a nationwide epidemiological study to get a reliable estimate of the prevalence and incidence of and insight into risk factors for HCV infection in HIV uninfected MSM.

Not surprising, all reported unprotected anal intercourse and most had concomitant other STI diagnose and six used non-injection drugs during sex. These are known risk factors for sexual HCV-transmission in HIV-*positive* MSM[19]. In the UK, the British Association of Sexual Health and HIV (BASHH) recommends to at least consider testing MSM for HCV if they are considered at high risk for HCV infection (independent of HIV-status)[20]. In the Netherlands guidelines for the STI clinics advise testing HIV positive MSM and MSM notified for HCV, MSM diagnosed with a lymphogranuloma venereum infection and MSM refusing an HIV test[21]. In Belgium, there is no national guideline for HCV-testing in HIV-negative MSM. Our case series, together with the high prevalence of chronic HCV infection in the AmPREP project[14], call for HCV testing of MSM at Dutch and Belgian STI clinics in order to get reliable data of the HCV prevalence and incidence in 2018. PrEP programs should include regular HCV testing and MSM who start using PrEP outside the context of an official PrEP program should be tested at STI clinics[22]. In a recently published systematic review, daily oral PrEP use was associated with a significant increase in rectal chlamydia and increase in any STI diagnosis[23], which emphasises the need for STI as well as HCV prevention strategies for PrEP users and their partners.

Second, as multiple parties are involved in the care for MSM (HIV centres, STI clinics, general practitioners) collaboration is needed if HCV elimination is to be pursued. Last but not least, the development and validation of a HCV-risk score for HIV-negative MSM, as has been done before for HIV infected MSM, could facilitate targeted HCV testing in the future[24].

According to the definition for acute HCV infection by the European AIDS Treatment Network (NEAT) consensus panel(1), all our patients fulfilled the criteria for acute HCV, except for one patient in whom, an earlier negative test was missing. And although he was 'directly' diagnosed after a recent partner notification, we cannot say for sure that he had an acute infection. Perhaps this patient is better defined as a recent infection according to definitions of Hajarizadeh et al.(2).

Our case series has several limitations. Because our cases were not identified during a prospective surveillance study, risk factors for HCV infection cannot be identified as we cannot compare our cases with HCV negative controls. Furthermore, we have no denominator and therefore no estimate of the prevalence and incidence can be given. Also, we report on Dutch and Belgium cases. This is due to the fact that the acute HCV treatment study (DAHHS) is recruiting patients in both neighbouring countries. Although the healthcare systems in both countries are very alike, two important differences should be mentioned. In Belgium HCV therapy for patients with F0 to F2 fibrosis is currently restricted to patients that are HIV/HCV–coinfected, while in the Netherlands restrictions are no longer in place. In contrast, at the time of writing of this manuscript PrEP was available free of charge in Belgium but not in the Netherlands, except for a small group of MSM participating in the AmPREP program.

In conclusion, in the changing landscape of TasP and PrEP, close monitoring of HCV infection among HIV-uninfected MSM is needed to improve case finding of HCV infection and decide upon the best testing policies of HCV infection in HIV-negative MSM.

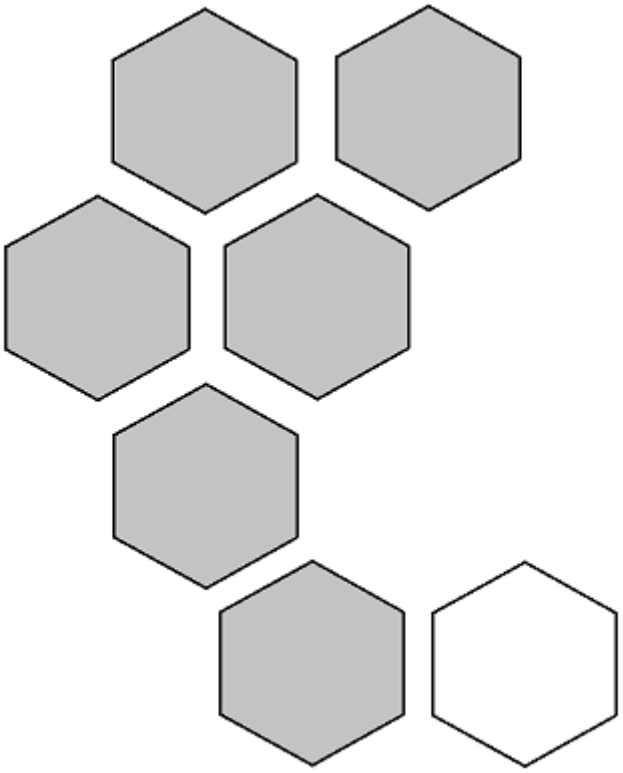
References

1. (WHO). WHO. Combating Hepatitis B and C to reach elimination by 2030. . Geneva: WHO; May 2016 Available from: http://appswhoint/iris/bitstream/10665/206453/1/WHO_HIV_201604_engpdf?ua=1.
2. Platt L, Easterbrook P, Gower E, et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. Lancet Infect Dis 2016;16:797-808.
3. Boerekamps A NAM, Smit C, Arends JE, Richter C, Reiss P, Rijnders BJ, Brinkman K, van der Valk M. High treatment uptake in HIV/HCV-coinfected patients after unrestricted access to direct-acting antivirals in the Netherlands. CID, in press 2017.
4. Boerekamps A VdBG, Lauw FN, Leyten EM, Van Kasteren ME, van Eeden A, Posthouwer D, Claassen MA, Dofferhoff AS, Verhagen DWM, Bierman WF, Lettinga KD, Kroon FP, Delsing CE, Groeneveld PH, Soetekouw R, Peters EJ, Hullegie SJ, Popping S, Van de Vijver DAMC, Boucher CA, Arends JE, Rijnders BJ,. Declining HCV incidence in Dutch HIV positive men who have sex with men after unrestricted access to HCV therapy. CID, in press 2017.
5. Ghisla V, Scherrer AU, Nicca D, Braun DL, Fehr JS. Incidence of hepatitis C in HIV positive and negative men who have sex with men 2000-2016: a systematic review and meta-analysis. Infection 2016.
6. Urbanus AT, Van De Laar TJ, Geskus R, et al. Trends in hepatitis C virus infections among MSM attending a sexually transmitted infection clinic; 1995-2010. Aids 2014;28:781-90.
7. Gotz HM, van Doornum G, Niesters HG, den Hollander JG, Thio HB, de Zwart O. A cluster of acute hepatitis C virus infection among men who have sex with men--results from contact tracing and public health implications. Aids 2005;19:969-74.
8. Rodger AJ, Cambiano V, Bruun T, et al. Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy. Jama 2016;316:171-81.
9. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. N Engl J Med 2016;375:830-9.
10. Molina JM, Capitant C, Spire B, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. N Engl J Med 2015;373:2237-46.
11. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet 2016;387:53-60.
12. http://www.prepineurope.org/en/. Accessed at 19-02-2018. .
13. MacGregor L, Martin NK, Mukandavire C, et al. Behavioural, not biological, factors drive the HCV epidemic among HIV-positive MSM: HCV and HIV modelling analysis including HCV treatment-as-prevention impact. Int J Epidemiol 2017.
14. Hoornenborg E, Achterbergh RCA, Schim Van Der Loeff MF, et al. Men who have sex with men starting pre-exposure prophylaxis (PrEP) are at risk of HCV infection: evidence from the Amsterdam PrEP study. Aids 2017.
15. Yaphe S, Bozinoff N, Kyle R, Shivkumar S, Pai NP, Klein M. Incidence of acute hepatitis C virus infection among men who have sex with men with and without HIV infection: a systematic review. Sex Transm Infect 2012;88:558-64.
16. Ireland G HS, Goorney B et al. Evaluation of hepatitis C testing in men who have sex with men, and associated risk behaviours, in Manchester, UK. Sex Transm Infect 2017;93:404-9.
17. van de Laar TJ, Paxton WA, Zorgdrager F, Cornelissen M, de Vries HJ. Sexual transmission of hepatitis C virus in human immunodeficiency virus-negative men who have sex with men: a series of case reports. Sex Transm Dis 2011;38:102-4.
18. McFaul K, Maghlaoui A, Nzuruba M, et al. Acute hepatitis C infection in HIV-negative men who have sex with men. J Viral Hepat 2015;22:535-8.
19. Vanhommerig JW, Lambers FA, Schinkel J, et al. Risk Factors for Sexual Transmission of Hepatitis C Virus Among Human Immunodeficiency Virus-Infected Men Who Have Sex With Men: A Case-Control Study. Open forum infectious diseases 2015;2:ofv115.

20. Fitzpatrick C P-SN, Williams D, Richardson D. Acute hepatitis C in HIV-uninfected men who have sex with men who do not report injecting drug use. Int J STD AIDS 2017;28:1158.
21. RIVM. Het consult seksuele gezondheid, Draaiboek. . Available from: https://lcirivmnl/draaiboeken/consult-seksuele-gezondheid November, 2016.
22. NVHB. Nederlandse richtlijn HIV Pre-expositie profylaxe. Available from: http://nvhbnl/richtlijnen/ September 2016. .
23. Traeger MW, Schroeder SE, Wright EJ, et al. Effects of Pre-exposure Prophylaxis for the Prevention of HIV Infection on Sexual Risk Behavior in Men Who Have Sex with Men: A Systematic Review and Meta-analysis. Clin Infect Dis 2018.
24. Newsum AM, Stolte IG, van der Meer JT, et al. Development and validation of the HCV-MOSAIC risk score to assist testing for acute hepatitis C virus (HCV) infection in HIV-infected men who have sex with men (MSM). Euro Surveill 2017;22.

Part C

Is micro-elimination of HCV in Dutch HIV-positive MSM possible in the era of direct-acting anti-viral therapy?



Chapter 7

Is hepatitis C virus elimination possible among people living with HIV and what will it take to achieve it?

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Abstract

Introduction

The World Health Organization targets for hepatitis C virus (HCV) elimination include a 90% reduction in new infections by 2030. Our objective is to review the modelling evidence and cost data surrounding feasibility of HCV elimination among people living with HIV (PLWH), and identify likely components for elimination. We also discuss the real-world experience of HCV direct acting antiviral (DAA) scale-up and elimination efforts in the Netherlands.

Methods

We review modelling evidence of what intervention scale-up is required to achieve WHO HCV elimination targets among HIV-infected (HIV+) people who inject drugs (PWID) and men who have sex with men (MSM), review cost-effectiveness of HCV therapy among PLWH and discuss economic implications of elimination. We additionally use the real-world experience of DAA scale-up in the Netherlands to illustrate the promise and potential challenges of HCV elimination strategies in MSM. Finally, we summarize key components of the HCV elimination response among PWLH.

Results and discussion

Modeling indicates HCV elimination among HIV+ MSM and PWID is potentially achievable but requires combination treatment and either harm reduction or behavioral risk reductions. Preliminary modeling indicates elimination among HIV+ PWID will require elimination efforts among PWID more broadly. Treatment for PLWH and high-risk populations (PWID and MSM) is cost-effective in high-income countries, but costs of DAAs remain a barrier to scale-up worldwide despite the potential low production price ($50 per 12 week course). In the Netherlands, universal DAA availability led to rapid uptake among HIV+ MSM in 2015/16, and a 50% reduction in acute HCV incidence among HIV+ MSM from 2014 to 2016 was observed. In addition to HCV treatment, elimination among PLWH globally also likely requires regular HCV testing, development of low-cost accurate HCV diagnostics, reduced costs of DAA therapy, broad treatment access without restrictions,

close monitoring for HCV reinfection and retreatment, and harm reduction and/or behavioral interventions.

Conclusions

Achieving WHO HCV Elimination targets is potentially achievable among HIV-infected populations. Among HIV+ PWID, it likely requires HCV treatment scale-up combined with harm reduction for both HIV+ and HIV- populations. Among HIV+ MSM, elimination likely requires both HCV treatment and behavior risk reduction among the HIV+ MSM population, the latter of which to date has not been observed. Lower HCV diagnostic and treatment costs will be key to ensuring scale-up of HCV testing and treatment without restriction, enabling elimination.

Introduction

Viral hepatitis was the seventh leading cause of death worldwide in 2013, increasing from the tenth leading cause in 2010[1]. The vast majority of morbidity and mortality attributable to viral hepatitis is due to hepatitis C virus (HCV) and hepatitis B Virus (HBV). In response to this increasing public health challenge, the World Health Organization recently released targets for HBV and HCV elimination by 2030 (see table 1)[2]. Elimination is traditionally defined as a reduction to zero in the incidence of disease in a specific population or geographical location, with continued prevention efforts required to prevent the re-establishment of transmission[3]. Given this strict definition of elimination would require substantial economic and political resources and could be unattainable in most settings, the goal of 'elimination' is often flexibly defined. The recent WHO elimination "as a public health threat" targets are comprised of a 90% relative reduction in new infections and a 65% relative reduction in hepatitis-related mortality by 2030.

Table 1 WHO hepatitis elimination goals: impact and service coverage targets[2]

WHO Impact Targets by 2030	
Incidence: New cases of chronic HBV and HCV	90% relative reduction
Mortality: HBV and HCV deaths	65% relative reduction
WHO Service Coverage Targets by 2030	
HBV childhood vaccination coverage	90%
HBV birth dose vaccination coverage or other prevention of mother to child transmission initiative	90%
Screening of blood donations	100%
Safe injections: % of injections administered with safety engineered devices in and out of health facilities	90%
Harm reduction: number of sterile needles and syringes provided per person who inject drugs per year	300
HBV and HCV diagnosis	90%
HBV and HCV treatment	80% of persons with chronic infection treated

Hence, to achieve the WHO incidence elimination targets, efforts must focus on both prevention of *disease* and prevention of *transmission*. The advent of highly-effective HCV DAA therapy, with sustained viral response (SVR) exceeding 90% in both HCV monoinfected and HIV/HCV coinfected populations[4-8] has renewed optimism that substantial reductions or elimination of end stage liver disease and HCV-related mortality is a possibility. The widespread use of HIV antiretroviral treatment for prevention has also led to speculation that HCV treatment could also be used for prevention. Additionally, among people who inject drugs (PWID), a key risk group for HCV, harm reduction interventions such as opiate substitution therapy (OST) and needle and syringe programs (NSP) have been the traditional backbone of HCV prevention. A recent Cochrane systematic review[9] found that OST reduces risk of HCV acquisition by 50% (risk ratio 0.50 95% CI 0.40-0.63) and combined with high coverage of NSP results in a 71% reduction in the risk of HCV acquisition (Risk Ratio=0.29 95% CI=0.13-0.65).

The WHO strategy does not include discussion relating to elimination of viral hepatitis among HIV-infected populations specifically. Yet, because of the shared transmission routes many people living with HIV (PLWH) are coinfected with viral hepatitis. Globally, approximately 6.2% (3.4-11.9%) of PLWH are coinfected with HCV, equating to approximately 2.28 million (IQR 1.27-4.42) HIV/HCV coinfected individuals[10]. Indeed, people living with HIV (PLWH) are six times more likely to be infected with HCV compared to those not infected with HIV. The burden of HIV-HCV coinfection is particularly high among high risk groups such as men who have sex with men (MSM) and people who inject drugs (PWID). Among HIV-infected individuals worldwide, it has been estimated that 2.4% (IQR 0·8-5·8) are coinfected with HCV within general population samples, yet this rises to 6.4% (3.2-10.0) in men who have sex with men (MSM), and 82.4% (55.2-88.5) in people who inject drugs (PWID)[10]. As such, to achieve the WHO HCV elimination incidence reduction target among PWLH it is crucial to tackle transmission among HIV-infected MSM and PWID. However, although the prevention interventions required to eliminate HCV globally will be equally applicable to coinfected populations, the intervention level required and targeting may be different based on specific epidemic characteristics.

The objective of this paper is to review the modelling and cost evidence surrounding feasibility of HCV elimination among HIV-infected (HIV+) key populations such as men who have sex with men (MSM) and people who inject drugs (PWID) and identify the likely components required for HCV elimination among PLWH. We use the real world experience of HCV direct acting antiviral (DAA) scale-up in the Netherlands through the Dutch Acute HCV in HIV Studies to illustrate the promise and potential challenges of HCV elimination strategies in a key population (MSM).

Methods

This analysis is comprised of four parts:

1. A review of the theoretical mathematical modeling literature examining what prevention and treatment scale-up is required for HCV elimination among HIV-infected PWID and HIV-infected MSM populations.
2. A review of the cost-effectiveness of HCV treatment for HIV-infected populations and discussion of cost considerations for elimination.
3. A discussion of the real-world experience of HCV DAA scale-up among HIV+ MSM in the Netherlands
4. A summary of probable and possible components of the HCV elimination response among PWLH.

Results and discussion

Modeling the scale-up needed for HCV elimination among HIV-infected populations

1. HIV-infected people who inject drugs (PWID)

Numerous burden of disease models have shown that existing or modestly increased levels of treatment targeted at individuals with more advanced liver disease can achieve the WHO HCV mortality target (65% reduction by 2030) in a variety of global settings. For example, a

regional European Union model showed that HCV treatment only need to increase from 150,000 patients in 2015 to 187,000 patients in 2025 to achieve the mortality elimination target[11]. A separate multi-country analysis including some resource limited settings found that achieving the WHO HCV mortality target in Hungary, Indonesia, Lebanon, Pakistan, and Romania is unlikely to be achieved with existing screening/treatment programs, but could be achieved with scaled-up screening and treatment[12]. These models of disease progression are particularly valuable in identifying the level and targeting of treatment required to reduce HCV mortality, but because they do not mechanistically incorporate disease transmission are unable to shed light on what is required to achieve the WHO incidence elimination target.

A wide body of literature since 2011 has utilized epidemic modeling to explore what level of prevention scale-up could result in control and elimination among PWID, and whether HCV treatment could be used for prevention. Several initial modeling studies in the UK and general PWID populations of varying prevalences have indicated that harm reduction alone is unlikely to achieve HCV elimination among PWID populations[13,14]. Subsequent studies have explored the potential of HCV treatment as prevention among PWID populations in a range of settings including North America, Europe, Asia, and Australia[13,15-20]. Broadly speaking, these studies have generally found that scale up of HCV treatment to rates to below 100 per 1000 PWID annually, particularly in combination with harm reduction[13,16,21], can reduce HCV incidence by 90% by 2030 across a wide range of settings. Results have been consistent between high and low income settings examined, such as Vietnam[20].

Additionally, modeling studies have pointed to several key additional elements which are required for achieving elimination among PWID: One Australian study highlighted the need for enhanced HCV screening among PWID in order to sustain HCV treatment rates required for elimination, a situation which is likely applicable to many global settings[22]. Additionally, a modeling study in the rural U.S. emphasized the importance of retreatment of reinfection in achieving elimination targets[21]. As such, elimination strategies likely require regular testing[22], HCV treatment[13,15-20], harm reduction[13,16,21], and retreatment of reinfections[21].

Despite several studies modeling HIV and HCV coinfection transmission among PWID[23,24], to our knowledge as of 2017 no published study has explored what is required for HCV elimination among HIV-infected PWID in particular. Preliminary modeling presented at a recent international conference indicated that HCV treatment targeted at HIV-infected PWID in Andalusia, Spain would not achieve elimination among this population due to continued risk of HCV transmission from HIV-negative PWID populations[25]. Therefore, more generally, because the burden of HCV is high among HIV-uninfected PWID populations, and as HIV-infected PWID populations are likely to mix with HIV-uninfected PWID populations, elimination among HIV-infected PWID is probably only achievable if combination HCV prevention efforts are targeted both HIV+ and HIV- PWID populations.

2. HIV-infected men who have sex with men (MSM)

An HCV epidemic among HIV-infected MSM has been observed in the United States, Western Europe, Australia, Taiwan, Hong Kong, and Japan, with HCV incidence and prevalence among HIV-infected MSM substantially higher than the HIV-uninfected MSM population[26,27]. A growing number of modeling studies since 2015 have explored what level of intervention (treatment and/or risk reduction) is required to eliminate HCV among HIV-infected MSM populations[28-31]. To date, these studies have focused exclusively on Western European settings (UK, Switzerland, Berlin, and the Netherlands), and no studies have explored resource limited settings, in part because of the lack of epidemiological data on HCV epidemics among HIV+ MSM in these settings. However the specific epidemic characteristics between the modelled settings has varied. One unifying characteristic is the relatively low rates of primary incidence among HIV+ MSM (1-2 per 100 person-years[26,32]) compared to PWID populations but high rates of reinfection (2-10 fold that of primary incidence[33-35]) Together these could pose a challenge for elimination efforts, where a relative reduction of 90% would translate to very low targets (0.1-0.2/100 person-years) which could be particularly hampered by high rates of reinfection. Nevertheless, the absolute numbers of HCV-HIV coinfected MSM are small, most diagnosed HIV+ MSM are linked to care in high income settings where HCV epidemics among HIV+ MSM have been documented [36-38] so HCV elimination may be particularly feasible in this group.

As with PWID, modeling indicates the level of intervention required among HIV+ MSM to achieve the WHO elimination targets varies by epidemiological setting, particularly given substantial variation of incidence trends. For example, among HIV+ MSM incidence of HCV over the past decade has remained relatively stable in the UK and the Netherlands. In the UK, a modeling study indicated that scaled-up rates of DAA therapy (from 46% to 80% treated within a year of diagnosis and from 7%/year to 20%/year thereafter) could reduce incidence among HIV+ MSM over 60% by 2030, but could not meet elimination targets[28]. Elimination targets could be reached when all those diagnosed receive treatment within 1 year of diagnosis, or if treatment scale-up is combined with a behavioral risk reduction[25].

By contrast, HCV incidence among HIV+ MSM has steadily increased over the past decade in Switzerland and Germany. In Switzerland, this has occurred alongside an increase in self-reported risk behavior (unprotected anal intercourse). A recent modeling study in Switzerland projected that if these trends continue, elimination (or even reductions in HCV incidence) could not be achieved through HCV treatment alone, and requires additional reduction of high risk behavior (perhaps through behavioral interventions)[29]. Preliminary modeling in Berlin supports the Swiss findings. Germany is a unique setting in that universal access for DAAs has been available since 2014, and as such relatively high treatment rates (>80% HIV+ MSM treated after their acute diagnosis) have been achieved. However, the continued increase in HCV incidence among HIV+ MSM in Berlin and Germany overall (from 0.33/100py in 1996-1999 to 2.28/100py in 2008-2012 in Germany[39]) and high levels of reinfection (7-8 per 100 person-years[33]) mean that elimination by 2030 likely requires both further scale-up of HCV treatment and reductions in high risk behavior[31].

Finally, preliminary modeling in the Netherlands indicated immediate treatment of all diagnosed HIV+ MSM with DAAs could only result in moderate reductions in HCV incidence among HIV+ MSM (~30% within 15 years), but not reach WHO elimination targets[30]. However, the real-world observation of a halving of HCV incidence among HIV+ MSM from 2014 to 2016 with expansion of DAA therapy as described below has raised excitement about the potential for elimination via treatment as prevention among HIV+ MSM in the Netherlands, described later in this paper.

Cost and cost-effectiveness implications of HCV testing and treatment scale-up for elimination among HIV-infected populations

There is a wide body of evidence that HCV treatment is cost-effective for HIV-infected populations, including HIV+ MSM with a risk of reinfection, [40-44] in high income settings such as the United States and the UK. Additionally, as mentioned previously, achieving HCV elimination among key risk groups such as HIV+ PWID, may require targeting the broader PWID population. Numerous economic evaluations have shown that HCV treatment is cost-effective for PWID populations in high-income settings [45-53] despite the potential risk of reinfection and higher mortality rates among PWID populations. Indeed, economic evaluations indicate treating PWID with an ongoing risk of transmission may accrue substantial economic benefits through prevention of transmission. Additionally, an economic analysis in Australia found that HCV treatment scale-up to achieve the WHO targets among PWID was cost-effective[15]. Unfortunately, no cost-effectiveness studies for HIV-infected populations or PWID have been performed in resource limited settings. However economic analyses have shown that DAA therapy for the general population is cost-effective India[54] and Egypt[55,56] where generic or low cost DAAs are available.
Despite the evidence HCV treatment is cost-effective, the high costs of HCV treatment [57] (>$75,000 per 12 week treatment course for sofosbuvir+daclatasvir in the US and UK) remain a major barrier to HCV treatment scale-up. Prices vary widely depending on country and income status[57], and prices of innovator and generic medicines have fallen, but nevertheless remain prohibitively high for widespread scale-up in developed and developing countries alike.

Unfortunately, the high costs of HCV treatment have so far resulted in prioritization of HCV therapy (or restrictions on insurance reimbursement) even in developed countries[58,59]. In these settings, patients with more advanced liver disease and those coinfected with HIV have traditionally been prioritized for early treatment. Although this type of strategy will be effective in preventing HCV-related morbidity and mortality among PWLH, it undermines elimination efforts as PLWH will remain at risk of being infected or reinfected with HCV from individuals who remain untreated and are at risk of transmitting. For example, PWID

with a risk of transmission tend to be younger with less advanced liver disease, and therefore prioritization strategies targeting individuals with advanced liver disease may fail to prevent the substantial amount of transmission from this group[60]. This is despite economic assessments indicating that treatment scale-up among PWID at or below the level required for elimination is cost-effective in settings like Australia, the UK, and Netherlands[15,60,61]. Additionally, models indicate early treatment for PWID is cost-effective compared to delay until cirrhosis, and may be more cost-effective than early treatment for those with no ongoing risk in settings with low-moderate (20/40%) HCV prevalence among PWID due to substantial prevention benefits of early treatment of PWID[60]. Unfortunately, no economic evaluations have assessed whether scaled-up treatment to achieve HCV elimination among PWID is cost-effective in resource-limited settings.

However, although HCV therapy is likely cost-effective, the high costs per treatment results in a substantial budgetary impact in countries with a large HCV infected populations. This has resulted in HCV treatment restrictions even in resource rich countries in the U.S. and Europe[58,59]. Indeed, HCV treatment coverage is still low globally[62]. A recent analysis estimated that the percentage of people with HCV who were treated with DAAs in 2016 ranged from 8.1% in North America and North Africa/Middle East to 0.1% in sub-Saharan Africa[63]. Among 91 countries analyzed, 47 countries had more new HCV infections than individuals who achieved cure through HCV treatment in 2016[63], indicating that these countries are failing to turn off the tap of new infections with treatment. Nevertheless, some countries are achieving very high treatment rates among specific subpopulations, such as among HIV+ MSM in the Netherlands, discussed in the next section.

Promisingly, HCV DAA therapies could be produced as generics at a fraction of the current costs[64], particularly from within a country such as India due to its sizeable generic industry and low production costs. A recent analysis estimated the costs of generic HCV DAA production based on the costs of their active pharmaceutical ingredients. This analysis found that the combination treatment sofosbuvir and daclatasvir has an estimated generic cost of $50-72 per 12-week course with a 10-50% profit margin (Hill A, *unpublished results*).

Additionally, even the costs of HCV diagnosis and monitoring remain prohibitive in many developing countries[65]. For example, in India, generic HCV treatments are available for at or below $300 per treatment course, yet HCV antibody and RNA testing costs an estimated $17 and $108, respectively[66]. Additionally, with current treatment monitoring as suggested by the Indian national guidelines [67](every 4 weeks with RNA tests at week 0, 12, and SVR12) the cost of treatment delivery could easily far exceed that of HCV treatment.

Finally, in many settings additional financing will be required to build the capacity of health services for diagnosis and treatment of HCV. However, the economic implications of this health systems strengthening (in terms of increased personnel, training, infrastructure, etc) has not been estimated. It is possible that integration of HCV testing and treatment within HIV services will prove to be an effective and cost-effective approach[68,69].

HCV elimination among HIV-infected MSM in the real world: Dutch experience

In the Netherlands, surveillance data indicates that among PLWH, the vast majority of acute HCV infection diagnoses occur among MSM[70]. In this section, we detail the Dutch experience of HCV direct-acting antiviral (DAA) scale-up and impact on acute HCV incidence and HCV prevalence among HIV+ MSM.

HIV and HCV care is well-organized in the Netherlands. All patients diagnosed with HIV are cared for by a team of infectious diseases physicians and specially trained HIV nurses in 26 treatment centers spread across the country. Screening for chronic HCV is universal at entry into HIV care and more than 99% of the HIV infected patients in care in the Netherlands have been tested for HCV at least once[71]. Screening for incident HCV infections in MSM is performed by testing ALT (followed by HCV testing when a new ALT elevation is observed) twice a year. HCV/HIV coinfected MSM visit the HIV outpatient clinic at least twice a year. HCV infections can be treated by the infectious diseases physician so no referral to a hepatologist is needed. Facilitated by specially trained on-site data collectors, detailed clinical and laboratory data from consenting patients (98%) are registered in a central database, comprising the AIDS Therapy Evaluation in the Netherlands (ATHENA)

cohort. Additionally, two prospective acute HCV treatment studies among HIV+ individuals have occurred (Dutch Acute HCV in HIV Studies, DAHHS1 [from 2013-2014] and DAHHS2 [2016-ongoing]) [72,73] in 17 centers providing care for 75% of the Dutch HIV+ MSM population.

In the Netherlands, DAAs were available from September 2014 for HCV infected patients with significant liver fibrosis or cirrhosis, and October 2015 regardless of fibrosis stage. This led to a very rapid uptake of HCV therapy among HIV+ MSM in the ATHENA cohort, with 79% attaining SVR just 14 months after restrictions were lifted[74] and a substantial decrease in the pool of HCV RNA positive HIV infected MSM in care in the Netherlands. Indeed, while in 2015 4.1% (450 of 11070) of the HIV+ MSM in care were HCV RNA+, this decreased to 1.5% (176 of 11749) by the end of 2016. As of May 2017, less than 150 HCV infected HIV+ MSM remain to be treated. With only 1.5% of the HIV+ MSM population currently remaining HCV infected, HCV elimination may become a reality. However the residual group of infected patients is likely a more difficult to reach subgroup, and the risk of reinfection among HIV-positive MSM is high[33,34,75,76].

The data described above demonstrate that a very rapid decline in the *prevalence* of HCV can be achieved in a well-organized health care system of a resource rich country. However, to achieve HCV elimination according to the WHO targets, the *incidence* of new HCV infections needs to decrease by 90% by 2030[2]. We obtained data from the DAHHS studies to compare the incidence of acute HCV infections in the first year after universal DAA availability (2016) with the last year before DAA became available (2014). From 2014 to 2016, a 51% decrease in acute HCV infections was observed[77]. Furthermore, this decrease contrasted with a significant increase in the percentage of positive syphilis (+2.2%) and gonorrhea (+2.85%) tests in HIV-positive MSM observed at STD clinics across the country[78-80], indicating that the reduction in HCV was unlikely to be due to behavioral risk reduction.

While the substantial reduction in HCV incidence among HIV+ MSM observed after widespread scale-up of HCV treatment in the Netherlands is reason for optimism, an

observational study cannot prove a causal relationship. Further modeling work will be required to disentangle the estimated impact of HCV treatment as prevention initiatives among HIV+ MSM in the Netherlands, and coverage required for elimination. We consider it unlikely that HCV treatment as prevention alone will result in a 90% reduction in the incidence of HCV (the WHO target) among HIV+ MSM in the Netherlands, and discuss additional steps likely required in the following section. Indeed, no further decline in the HCV incidence has been observed in 2017 so far[81]. Additionally, we note that the Dutch experience is a specific example within a resource-rich country with well-coordinated HIV and HCV care. Whether the experience in the Netherlands will translate to other resource limited settings requires further study.

Probable and possible components required to achieve HCV elimination among PLWH

In summary, despite the promise of HCV elimination using HCV treatment as prevention from both theoretical modeling studies and real-world observations in the Netherlands, numerous *probable* and *possible* barriers exist which could hamper HCV elimination efforts among PLWH (Table 2). As such, the following components are likely an important part of the HCV elimination response among PWLH (based on *probable* barriers):

1. Regular HCV testing of high risk populations, both HIV+ and HIV-: Among HIV+ PWID, modeling indicates that elimination likely requires elimination efforts among the broader PWID population[25], yet worldwide an estimated 80% of HCV-infected individuals remain undiagnosed[62], a situation which may be worse among PWID. For example, in India only an estimated 5% of HCV-infected PWID are diagnosed[82]. Consequently the treatment scale-up required for elimination among PWID likely requires enhanced testing among both HIV+ and HIV- PWID [22]. Among HIV+ MSM, modeling indicates that regular testing of HIV+ MSM is also likely required for elimination. Testing of other MSM populations is described below under possible barriers.

2. Development of low cost, simple, reliable and accurate HCV diagnostics. Even in low-income countries with low cost DAAs, the price of HCV diagnostics remain a barrier[65]. Additionally, the currently available diagnostic products are complex, many which require a cold chain and/or show poor accuracy among HIV-infected individuals[83].

3. Reduced costs for DAA treatment. Despite the availability of generic and low-cost DAAs in some resource limited settings, costs of DAA therapy in the vast majority of countries remains a barrier to widespread scale-up of HCV treatment[57,84,85]. Greater market transparency and price negotiations are required[84].
4. Broad access to HCV treatment without restrictions: Modeling studies indicate that restricting treatment for those with more advanced fibrosis and/or by drug use status, as is occurring in many settings[58,59], will likely have limited impact on preventing transmission among PWID populations[86], the vast majority who are younger with less advanced disease. In settings where HCV epidemics are predominantly PWID-driven, broad access to HCV treatment regardless of disease stage is therefore required for HCV elimination. Even in settings with substantial general population transmission, it is likely that restricting treatment for more advanced disease stages will mean that substantially more treatments are required to achieve elimination[87].

5. Close monitoring for reinfection and retreatment of reinfections: Treating those at risk of transmission, the target group for HCV treatment as prevention efforts, will result in reinfections. Among PWID, lower rates of reinfection compared to primary infection were reported in the IFN-era[88], and reinfection rates among PWID on OST in DAA trials have been low (<3 per 100 person-years)[89]. However, modeling in a rural expanding epidemic setting in the United States indicates achieving the WHO elimination incidence target among PWID requires retreatment of reinfections[21]. Among HIV+ MSM, European studies indicate high incidence of HCV reinfection in HIV+ MSM (2-10 fold that of primary infection rates) in both the IFN-era [33,34,76] and DAA era [75]. As modeling studies have shown that more frequent testing for HCV and earlier initiation of HCV treatment could reduce the HCV epidemic among HIV-positive MSM [31,90] and given that those previously infected with HCV are a particularly high risk sub-

population for transmission, reducing the time from reinfection to retreatment is important. This could be achieved by increasing the frequency of HCV reinfection screening and may require out of the box diagnostic strategies like a home-based diagnostic approach in which the patient collects dried blot spots that are sent to the lab for HCV RNA or antigen testing.

6. Harm reduction and other behavioral interventions to prevent infection/reinfection: Despite the importance of harm reduction such as opiate substitution therapy and needle and syringe programs for preventing HCV infection among PWID[9], access to these interventions in many settings is poor, particularly in many resource limited settings[91]. Scale-up of harm reduction, as recommended by the WHO[2], is crucial. Additionally, among HIV+ MSM, effective behavioral interventions to prevent HCV infection are urgently required, as modeling from several settings indicates elimination of HCV in this population without effective behavioral intervention will be unlikely[29,31,92]. Unfortunately, there is a lack of robust evidence surrounding the efficacy of behavioral change interventions targeting HCV risk among HIV+ MSM. It is possible that some interventions developed to prevent HIV transmission among MSM may also be effective against HCV, particularly those targeting unprotected anal intercourse[29,93]. There is an emerging body of literature examining the development of educational and counseling interventions targeted at MSM who engage in ChemSex[94-96], which may reduce the risk of acquiring HCV among this population. Further research is needed examining the development, acceptability, and efficacy of culturally sensitive behavioral change interventions for preventing HCV infection.

Additionally, the following items would address *possible* barriers to elimination and therefore may be required for elimination among PWLH. We note that further evidence is required to support whether these items are necessary components of an elimination response:

1. Testing among HIV-negative MSM receiving HIV pre-exposure prophylaxis (PrEP): There is growing evidence of HCV infection among HIV-negative MSM receiving PrEP,

a group which could contribute to HCV transmission to HIV+ MSM. In Amsterdam, the prevalence of chronic HCV among HIV-negative MSM in a PrEP implementation program was 4% (15/375), comparable to the prevalence of 4.2% in HIV+ MSM[97]. In Antwerp, Belgium, HCV prevalence among HIV-negative MSM at the start of a PrEP project was 2%, and several new HCV infections were diagnosed during follow-up in these PrEP users (B Rijnders, personal communication). The extent to which HIV-negative MSM (particularly on PrEP) contribute or will contribute to the HCV epidemic among HIV+ MSM in unclear, but increased epidemiological surveillance will shed light on the burden of disease in this group and help understand their potential importance to the HIV+ MSM epidemic.

2. Coordinated multi-country prevention and treatment effort: Among HIV+ PWID, the contribution of cross-border transmission and import/export of infections to the epidemic is unclear. Among HIV+ MSM, the highly connected nature of the HCV epidemic among HIV+ MSM in Western Europe and frequent travel of MSM between European cities has been documented[98,99]. Therefore, at least in Europe, local elimination of HCV among HIV+ MSM may require coordinated multi-country efforts.

3. Licensing for treatment in the acute stage: Currently none of the approved DAA regimens are licensed for the treatment of acute HCV. Depending on the regional legislations, this may result in a compulsory "wait for documented chronicity" policy and thus increase the duration of time for onwards HCV transmissions to occur. HIV modeling studies have highlighted the importance of the acute HIV stage on the HIV epidemic[100]. However, the importance of acute HCV infection in relation to the HCV epidemic among PLWH is unclear and further research is needed to determine to what degree and in what populations early treatment is required for achieving elimination targets.

4. Monitor if transmission of HCV clones with acquired DAA resistance occurs: It was recently shown that the HCV Q80K polymorphism, associated with DAA resistance, is frequently detected and transmitted among HIV+ MSM in the Netherlands [101]. As

relapse with documented DAA resistance is rare, the chance of a patient developing ánd transmitting acquired DAA resistance is theoretically small and as far as we know has only been described in the context of treatment with a first generation protease inhibitor[102]. As such, further research is needed to ascertain the importance of resistance in the DAA era.

Conclusions

Both theoretical modeling studies and emerging real world evidence from the Netherlands indicate that HCV elimination among HIV-infected key populations such as MSM and PWID is potentially achievable.

Due to a number of factors, elimination of HCV among HIV+ MSM may be complex; and require both high coverage HCV treatment and behavioral interventions. Elimination among HIV+ PWID will likely require elimination efforts among PWID more broadly. In addition to HCV treatment as prevention initiatives, elimination among PLWH also likely requires regular HCV testing, development of low-cost accurate HCV diagnostics, reduced costs of DAA therapy, broad treatment access without restrictions, close monitoring for HCV reinfection and retreatment, and harm reduction and/or behavioral interventions. Finally, we note that the vast majority of existing research is limited to high income settings, and more research is required relating to HCV elimination among PLWH in resource limited settings. For example, more modeling work is needed to assess what scale-up is required for HCV elimination among PLWH populations in resource-limited settings where transmission routes may vary and the HCV epidemics among HIV-infected populations may differ. Many developing countries have high burdens of injecting drug use as well as high HCV among HIV-infected PWID[10,103]. Yet, their risks may be different from high income settings. For example, an increasing number of analyses are focusing on HCV elimination among the general population in low or middle-income country settings such as Georgia and Pakistan[87,104], which have shown that even in settings with high numbers of PWID, transmission may be highly disseminated, with PWID experiencing risk both from

injecting drug use and the broader community through iatrogenic transmission. Hence, the requirements for elimination in these settings where PWID experience multiple risks may be different than in other settings.

Additionally, data are lacking on HCV among MSM in resource-limited settings, and as such the magnitude of the problem and requirements for elimination are unclear. In addition to differences in epidemic characteristics, clearly economic considerations across resource-limited countries will vary substantially, and as such the requirements for achieving HCV elimination among PWLH in these resource limited settings requires further study.

Table 2 Barriers to HCV elimination among PLWH

Probable barriers to HCV elimination among PLWH:
• Low levels of diagnosis in many settings and risk populations[62]
• Lack of availability of low cost, simple, reliable, and accurate HCV diagnostics for LMIC settings[65,83]
• High costs of DAA treatment[57]
• Restrictions on DAA accessibility by fibrosis stage and drug use status[58,59]
• Low levels of harm reduction availability for PWID in many settings[91]
• High reinfection incidence among HIV+ MSM[33,34,75,76]
• Lack of evidence-based interventions to reduce HCV infection among HIV+ MSM
Possible additional barriers:
• Transmission of HCV from HIV uninfected MSM, such as those on PrEP
• Spread of HCV clones with acquired DAA resistance[101]
• Lack of licensing for HCV treatment in the acute stage
• Cross border transmission of HCV, particularly among HIV+ MSM[98,99] and between countries with different levels of DAA availability

References

1. Stanaway JD, Flaxman AD, Naghavi M, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. The Lancet;388:1081-8.
2. World Health Organization. Global Health Sector Strategy on Viral Hepatitis, 2016-2021. 2016.
3. Dowdle WR. The principles of disease elimination and eradication

MMWR 1999;48:23-7.
4. Wyles D, Bräu N, Kottilil S, et al. Sofosbuvir and Velpatasvir for the Treatment of HCV in Patients Coinfected with HIV-1: an Open-Label, Phase 3 Study. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America 2017.
5. Wyles DL, Ruane PJ, Sulkowski MS, et al. Daclatasvir plus sofosbuvir for HCV in patients coinfected with HIV-1. N Engl J Med 2015;373:714-25.
6. Sulkowski MS, Eron JJ, Wyles DL, et al. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. JAMA 2015;313:1223-31.
7. Naggie S, Cooper C, Saag M, et al. Ledipasvir and sofosbuvir for HCV in patients coinfected with HIV-1. N Engl J Med 2015;373:705-13.
8. Bhattacharya D, Belperio PS, Shahoumian TA, et al. Effectiveness of All-Oral Antiviral Regimens in 996 Human Immunodeficiency Virus/Hepatitis C Virus Genotype 1-Coinfected Patients Treated in Routine Practice. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America 2017;64:1711 - 20.
9. Platt L, Reed J, Minozzi S, et al. Effectiveness of needle/syringe programmes and opiate substitution therapy in preventing HCV transmission among people who inject drugs. The Cochrane database of systematic reviews 2016;2016:CD012021.
10. Platt L, Easterbrook P, Gower E, et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. The Lancet Infectious Diseases;16:797-808.
11. Razavi H, Robbins S, Zeuzem S, et al. Hepatitis C virus prevalence and level of intervention required to achieve the WHO targets for elimination in the European Union by 2030: a modelling study. The Lancet Gastroenterology & Hepatology;2:325-36.
12. Alfaleh FZ, Nugrahini N, Matičič M, et al. Strategies to manage hepatitis C virus infection disease burden – volume 3. Journal of Viral Hepatitis 2015;22:42-65.
13. Martin N, Hickman M, Hutchinson S, Goldberg D, Vickerman P. Combination interventions to prevent HCV transmission among people who inject drugs: modelling the impact of antiviral treatment, needle and syringe programmes, and opiate substitution therapy. Clin Infec Dis 2013;57:S39-S45.
14. Vickerman P, Martin N, Turner K, Hickman M. Can needle and syringe programmes and opiate substitution therapy achieve substantial reductions in HCV prevalence? Model projections for different epidemic settings. Addiction 2012;107:1984-95.
15. Scott N, McBryde ES, Thompson A, Doyle JS, Hellard ME. Treatment scale-up to achieve global HCV incidence and mortality elimination targets: a cost-effectiveness model. Gut 2016.
16. Gountas I, Sypsa V, Anagnostou O, et al. Treatment and primary prevention in people who inject drugs for chronic hepatitis C infection: Is elimination possible in a high prevalence setting? Addiction 2017;doi: 10.1111/add.13764. [Epub ahead of print].
17. Cousien A, Tran VC, Deuffic-Burban S, Jauffret-Roustide M, Dhersin J-S, Yazdanpanah Y. Hepatitis C Treatment as Prevention of Viral Transmission and Liver-related Morbidity in Persons Who Inject Drugs. Hepatology 2015;(in press) DOI: 10.1002/hep.28227.
18. Martin NK, Vickerman P, Grebely J, et al. HCV treatment for prevention among people who inject drugs: modeling treatment scale-up in the age of direct-acting antivirals. Hepatology 2013;58:1598-609.
19. Lima VD, Rozada I, Grebely J, et al. Are Interferon-Free Direct-Acting Antivirals for the Treatment of HCV Enough to Control the Epidemic among People Who Inject Drugs? PLOS ONE 2015;10:e0143836.
20. Durier N, Nguyen C, White LJ. Treatment of Hepatitis C as Prevention: A Modeling Case Study in Vietnam. PLoS ONE 2012;7:e34548.

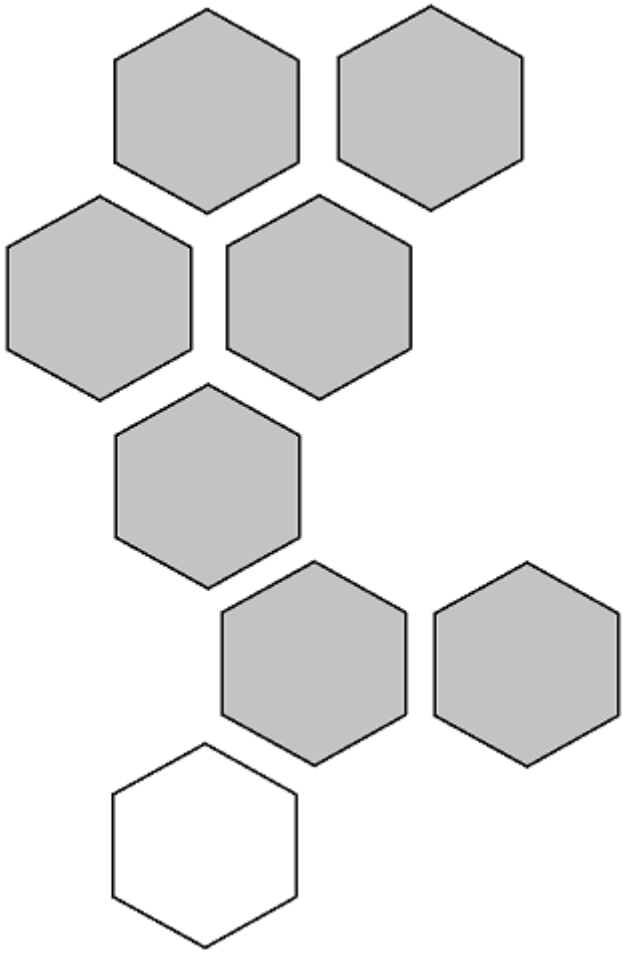
21. Fraser H, Zibbell J, Hoerger T, et al. Scaling-up HCV prevention and treatment interventions in rural United States— model projections for tackling an increasing epidemic. Addiction:n/a-n/a.
22. Scott N, Doyle JS, Wilson DP, et al. Reaching hepatitis C virus elimination targets requires health system interventions to enhance the care cascade. International Journal of Drug Policy;47:107-16.
23. Vickerman P, Martin NK, Hickman M. Understanding the trends in HIV and hepatitis C prevalence amongst injecting drug users in different settings—Implications for intervention impact. Drug and Alcohol Dependence 2012;123:122-31.
24. Birger RB, Le T, Kouyos RD, Grenfell BT, Hallett TB. The impact of HCV therapy in a high HIV-HCV prevalence population: A modeling study on people who inject drugs in Ho Chi Minh City, Vietnam. PLOS ONE 2017;12:e0177195.
25. Martin N. Is viral hepatitis elimination possible and what will it take to achieve it? 4th International HIV/Viral Hepatitis Coinfection Meeting 2017 Paris, France 23 July 2017 2017.
26. Hagan H, Jordan AE, Neurer J, Cleland C. Incidence of sexually transmitted hepatitis C virus infection in HIV-positive men who have sex with men. AIDS 2015;29:2335-45.
27. Jordan AE, Perlman DC, Neurer J, Smith DJ, Des Jarlais DC, Hagan H. Prevalence of hepatitis C virus infection among HIV+ men who have sex with men: a systematic review and meta-analysis. International Journal of STD & AIDS 2016;[epub] DOI: 10.1177/0956462416630910 PMID: 26826159.
28. Martin NK, Thornton A, Hickman M, et al. Can Hepatitis C Virus (HCV) Direct-Acting Antiviral Treatment as Prevention Reverse the HCV Epidemic Among Men Who Have Sex With Men in the United Kingdom? Epidemiological and Modeling Insights. Clinical Infectious Diseases 2016;62:1072-80.
29. Salazar-Vizcaya L, Kouyos RD, Zahnd C, et al. Hepatitis C virus transmission among human immunodeficiency virus-infected men who have sex with men: Modeling the effect of behavioral and treatment interventions. Hepatology 2016;64:1856-69.
30. Hullegie S, Nichols B, Rijnders B, et al. Is HCV Elimination Possible? A Modeling Study of HIV-Positive MSM. Conference on Retroviruses and Opportunistic Infections (CROI) 2016, Boston, Massachusetts Feb 22-25 2016;Abstract #536.
31. Martin N, Jansen K, Boesecke C, et al. Can HCV be eliminated among HIV-infected MSM in Berlin? Modeling a setting with increasing incidence and high treatment rates. American Association for the Study of Liver Diseases (AASLD), The Liver Conference 2017 Washington, DC 19-21 Oct 2017 2017
32. Yaphe S, Bozinoff N, Kyle R, Shivkumar S, Pai N, Klein M. Incidence of acute hepatitis C virus infection among men who have sex with men with and without HIV infection: a systematic review. Sex Trans Infec 2012;88:558-64.
33. Ingiliz P, Martin TC, Rodger A, et al. HCV reinfection incidence and spontaneous clearance rates in HIV-positive men who have sex with men in Western Europe. Journal of Hepatology;66:282-7.
34. Martin T, Martin N, Hickman M, et al. HCV reinfection incidence and treatment outcome among HIV-positive MSM in London. AIDS 2013;27:2551-7.
35. Chaillon A, Anderson C, Martin T, et al. INCIDENCE OF HEPATITIS C AMONG HIV-INFECTED MEN WHO HAVE SEX WITH MEN, 2000–2015. Conference on Retroviruses and Opportunistic Infections (CROI) 2017 Seattle, Washington Feb 13-16, 2017 Oral Abstract 134.
36. Rice BD, Delpech VC, Chadborn TR, Elford J. Loss to Follow-Up Among Adults Attending Human Immunodeficiency Virus Services in England, Wales, and Northern Ireland. Sexually transmitted diseases 2011;38:685-90.
37. Public Health England. HIV in the UK 2016 Report. https://wwwgovuk/government/uploads/system/uploads/attachment_data/file/602942/HIV_in_the_UK_reportpdf 2016.
38. Risher K, Mayer K, Beyrer C. The HIV treatment cascade in men who have sex with men, people who inject drugs and sex workers. Current opinion in HIV and AIDS 2015;10:420-9.
39. Jansen K, Thamm M, Bock C-T, et al. High Prevalence and High Incidence of Coinfection with Hepatitis B, Hepatitis C, and Syphilis and Low Rate of Effective Vaccination against Hepatitis B in HIV-Positive Men Who Have Sex with Men with Known Date of HIV Seroconversion in Germany. PLOS ONE 2015;10:e0142515.
40. Linas BP, Barter DM, Leff JA, et al. The cost-effectiveness of improved hepatitis C virus therapies in HIV/hepatitis C virus coinfected patients. AIDS 2014;28:365-76.

41. Campos N, Salomon J, Servoss J, et al. Cost-effectiveness of Treatment for Hepatitis C in an Urban Cohort Co-infected with HIV. Am J Med 2007;120:272-9.
42. Linas BP, Wong AY, Schackman BR, Kim AY, Freedberg KA. Cost-effective Screening for Acute Hepatitis C Virus Infection in HIV-Infected Men Who Have Sex With Men. Clinical Infectious Diseases 2012;55:279-90.
43. Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. Health Technol Assess 2011;15:1-210.
44. Hornberger J, Torriani FJ, Dieterich DT, et al. Cost-effectiveness of peginterferon alfa-2a (40kDa) plus ribavirin in patients with HIV and hepatitis C virus co-infection. J Clin Virol 2006;36:283-91.
45. Martin NK, Vickerman P, Miners A, et al. The cost-effectiveness of HCV antiviral treatment for injecting drug user populations. Hepatology 2012;55:49-57.
46. Sheerin IG, Green FT, Sellman JD. What is the cost-effectiveness of hepatitis C treatment for injecting drug users on methadone maintenance in New Zealand? Drug and Alcohol Review 2004;23:261 - 72.
47. Thompson Coon J, Castelnuovo E, Pitt M, Cramp M, Siebert U, Stein K. Case finding for hepatitis C in primary care: a cost utility analysis. Family Practice 2006;23:393-406.
48. Stein K, Dalziel K, Walker A, Jenkins B, Round A, Royle P. Screening for Hepatitis C in injecting drug users: A cost utility analysis. Journal of Public Health 2004;26:61-71.
49. Wong JB, Sylvestre Diana L, Siebert U. Cost-effectiveness of treatment of hepatitis C in injecting drug users. In: Jager J, Limburg W, Kretzszschmar M, Postma M, Wiessing L, eds. Hepatitis C and injecting drug use: impact, costs and policy options. Belgium: European Monitoring Centre for Drugs and Drug Addiction; 2004.
50. Leal P, Stein K, Rosenberg W. What is the cost utility of screening for hepatitis C virus (HCV) in intravenous drug users? J Med Screen 1999;6:124-31.
51. Vickerman P, Miners A, Williams J. Assessing the cost-effectiveness of interventions linked to needle and syringe programmes for injecting drug users. In: NICE, ed. London2008.
52. Martin NK, Vickerman P, Miners A, Hickman M. How cost-effective is hepatitis C virus treatment for people who inject drugs? Journal of Gastroenterology and Hepatology 2013;28:590-2.
53. Scott N, Iser DM, Thompson AJ, Doyle JS, Hellard ME. Cost-effectiveness of treating chronic hepatitis C virus with direct-acting antivirals in people who inject drugs in Australia. Journal of Gastroenterology and Hepatology 2016;31:872-82.
54. Aggarwal R, Chen Q, Goel A, et al. Cost-effectiveness of hepatitis C treatment using generic direct-acting antivirals available in India. PLOS ONE 2017;12:e0176503.
55. Elsisi GH, Aburawash A, Waked E. Cost-Effectiveness Analysis of New HCV Treatments in Egyptian Cirrhotic and Non-Cirrhotic Patients: A Societal Perspective. Value in Health Regional Issues 2017;13:7-15.
56. Obach D, Deuffic-Burban S, Esmat G, et al. Effectiveness and Cost-effectiveness of Immediate Versus Delayed Treatment of Hepatitis C Virus–Infected Patients in a Country With Limited Resources: The Case of Egypt. Clinical Infectious Diseases 2014;58:1064-71.
57. Iyengar S, Tay-Teo K, Vogler S, et al. Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis. PLOS Medicine 2016;13:e1002032.
58. Barua S, Greenwald R, Grebely J, Dore GJ, Swan T, Taylor LE. Restrictions for medicaid reimbursement of sofosbuvir for the treatment of hepatitis c virus infection in the united states. Annals of Internal Medicine 2015;163:215-23.
59. Marshall AD, Cunningham EB, Nielsen S, et al. Restrictions for reimbursement of interferon-free direct-acting antiviral drugs for HCV infection in Europe. The Lancet Gastroenterology & Hepatology.
60. Martin NK, Vickerman P, Dore GJ, et al. How should HCV treatment be prioritized in the direct-acting antiviral era? An economic evaluation including population prevention benefits. Journal of Hepatology 2016:DOI: 10.1016/j.jhep.2016.02.007.
61. van Santen DK, de Vos AS, Matser A, et al. Cost-Effectiveness of Hepatitis C Treatment for People Who Inject Drugs and the Impact of the Type of Epidemic; Extrapolating from Amsterdam, the Netherlands. PLOS ONE 2016;11:e0163488.

62. WHO. Global hepatitis report 2017. 2017.
63. Hill A, Nath S, Simmons B. The road to elimination of hepatitis C: analysis of cures versus new infections in 91 countries. Journal of Virus Eradication 2017;2017 (in press).
64. Hill A, Khoo S, Fortunak J, Simmons B, Ford N. Minimum Costs for Producing Hepatitis C Direct-Acting Antivirals for Use in Large-Scale Treatment Access Programs in Developing Countries. Clinical Infectious Diseases 2014;58:928-36.
65. Graham CS, Swan T. A path to eradication of hepatitis C in low- and middle-income countries. Antiviral Research 2015;119:89-96.
66. http://edos.metropolisindia.com/#/MetroEDOS.
67. Puri P, Anand AC, Saraswat VA, et al. Consensus Statement of HCV Task Force of the Indian National Association for Study of the Liver (INASL). Part II: INASL Recommendations for Management of HCV in India. Journal of Clinical and Experimental Hepatology 2014;4:117-40.
68. Solomon S. Cost-Saving Of Integrating HCV Testing Into HIV Testing Programs For PWID Using Respondent-Driven Recruitment. International Network on Hepatitis in Substance Users (INHSU) 2017 Jersey City, NJ Oral Poster Presentation 2017.
69. Ford N, Singh K, Cooke GS, et al. Expanding Access to Treatment for Hepatitis C in Resource-Limited Settings: Lessons From HIV/AIDS. Clinical Infectious Diseases 2012;54:1465-72.
70. van Sighem AI, Boender TS, Wit FWNM, Smit C, Matser A, P. R. Monitoring Report 2016. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. Stichting HIV Monitoring. Available online at wwwhiv-monitoringnl 2016.
71. Dutch Association of HIV-treating Physicians. National Dutch HIV Guideline, chapter 4.1. Available at: http://richtlijnhiv.nvhb.nl/index.php/Inhoud.
72. Hullegie SJ, Claassen MAA, van den Berk GEL, et al. Boceprevir, peginterferon and ribavirin for acute hepatitis C in HIV infected patients. Journal of Hepatology;64:807-12.
73. DAHHS2 study. www.clinicaltrials.gov/ct2/show/NCT01912495.
74. Boerekamps A, Newsom A, Smit C, et al. UNRESTRICTED DAA ACCESS IN THE NETHERLANDS: RAPID THERAPY UPTAKE IN HIV+HCV+ PATIENTS. Conference on Retroviruses and Opportunistic Infections (CROI) 2015 Seattle, Washington Feb 13-16 2017 Abstract 136.
75. Ingiliz P, Christensen S, Berger F, et al. HCV REINFECTION AFTER SUCCESSFUL DAA TREATMENT: A GECCO ANALYSIS. Conference on Retroviruses and Opportunistic Infections (CROI) 2017 Seattle, Washington Feb 13-16 2017 Abstract 567.
76. Lambers F, Prins M, Thomas M, et al. Alarming incidence of hepatitis C virus re-infection after treatment of sexually acquired acute hepatitis C virus infection in HIV-infected MSM. AIDS 2011;25:F21-F7.
77. Boerekamps A, van den Berk G, Lauw F, et al. SUBSTANTIAL DECLINE IN ACUTE HCV INFECTIONS AMONG DUTCH HIV+MSM AFTER DAA ROLL OUT. . Conference on Retroviruses and Opportunistic Infections (CROI) 2015 Seattle, Washington Feb 13-16 2017 Abstract 137LB 2017.
78. Wees VMvAFvOAvdBIOdCEHSHJdDCHBv. Sexually transmitted infections including HIV, in the Netherlands in 20162016.
79. A.A.M. van Oeffelen, I.V.F. van den Broek, E.L.M. Op de Coul, et al. Sexually transmitted infections including HIV, in the Netherlands in 2014. Rijksinstituut voor Volksgezondheid en Milieu RIVM 2015.
80. Visser M, van Aar F, van Oeffelen AAM, et al. Sexually transmitted infections including HIV, in the Netherlands in 2016. . Rijksinstituut voor Volksgezondheid en Milieu RIVM 2017.
81. Boerekamps A, Lauw FN, Leyten EM, et al. Declining HCV incidence in Dutch HIV positive men who have sex with men after unrestricted access to HCV therapy. Clinical Infectious Diseases (in press) 2017.
82. Solomon SS, Mehta SH, Srikrishnan AK, et al. High burden of HCV disease and poor access to HCV services among people who inject drugs in India: A cross-sectional study among 14,481 drug users across India. The Lancet Infectious diseases 2015;15:36-45.
83. Frontieres MS. Diagnosis and Treatment of Hepatitis C: A technical landscape. https://wwwmsfaccessorg/sites/default/files/MSF_assets/HepC/Docs/HepC_brief_TechnicalLandscape_ENG_2013pdf 2013.

84. WHO. Global report on access to hepatitis C treatment: Focus on overcoming barriers. http://appswhoint/iris/bitstream/10665/250625/1/WHO-HIV-201620-engpdf 2016.
85. Woode ME, Abu-Zaineh M, Perriëns J, Renaud F, Wiktor S, Moatti JP. Potential market size and impact of hepatitis C treatment in low- and middle-income countries. Journal of Viral Hepatitis 2016;23:522-34.
86. Harris RJ, Martin NK, Rand E, et al. New treatments for hepatitis C virus (HCV): scope for preventing liver disease and HCV transmission in England. Journal of Viral Hepatitis 2016:doi: 10.1111/jvh.12529.
87. Fraser H, al. e. Investigating the Impact of Scaling-Up Screening, Treatment, and Prevention Interventions Targeting Priority Groups for Hepatitis C Virus Elimination in Pakistan. International Network on Hepatitis in Substance Users (INHSU) 2017 Jersey City, NJ Poster Presentation 45 2017.
88. Aspinall A, Corson S, Doyle J, et al. Treatment of hepatitis C virus among people who are actively injecting drugs: a sysematic review and meta-analysis. Clinical Infectious Diseases 2013;57:S80-9.
89. Dore GJ. Hepatitis C Virus (HCV) Reinfection and Injecting Risk Behavior Following Elbasvir (EBR)/Grazoprevir (GZR) Treatment in Participants on Opiate Agonist Therapy (OAT): Co-STAR Part B. AASLD 2017 2017.
90. Popping S, van Kampen J, Verbon A, Boucher C, van de Vijver D. Intensive hepatitis C monitoring in previously HCV infected HIV-positive MSM is a cost saving method to reduce the HCV epidemic. . NCHIV 2016, abstract number O10, http://nchivorg/abstracts/, 2016 2016.
91. Mathers BM, Degenhardt L, Ali H, et al. HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. Lancet 2010;375:1014-28.
92. Martin N, Thornton A, Hickman M, et al. Can Hepatitis C Virus (HCV) Direct-Acting Antiviral Treatment as Prevention Reverse the HCV Epidemic Among Men Who Have Sex With Men in the United Kingdom? Epidemiological and Modeling Insights. Clinical Infectious Diseases 2016;62:1072-80.
93. Johnson W, Diaz R, Flanders W, et al. Behavioral interventions to reduce risk for sexual transmission of HIV among men who have sex with men. Cochrane Database of Systematic Reviews 2008:Art. No.: CD001230. DOI: 10.1002/14651858.CD001230.pub2.
94. Pakianathan MR, Lee MJ, Kelly B, Hegazi A. How to assess gay, bisexual and other men who have sex with men for chemsex. Sexually Transmitted Infections 2016;92:568-70.
95. Stuart D, Weymann J. ChemSex and care-planning: One year in practice. HIV Nursing 2015;15:24-8.
96. Stuart D. Sexualised drug use by MSM (ChemSex): a toolkit for GUM/HIV staff. HIV Nursing 2014;14:15.
97. Hoornenborg E, Achterbergh RCA, Schim van der Loeff MF, et al. MSM starting preexposure prophylaxis are at risk of hepatitis C virus infection. AIDS 2017;31:1603-10.
98. Network. TE. EMIS 2010: The European Men-Who-Have-Sex-With-Men Internet Survey, Findings from 38 countries. Stockholm: European Centre for Disease Prevention and Control; 2013.
99. van de Laar T, Pybus O, Bruisten S, et al. Evidence of a Large, International Network of HCV Transmission in HIV-Positive Men Who Have Sex With Men. Gastroenterology 2009;136:1609-17.
100. Powers K, Ghani A, Miller W, et al. The role of acute and early HIV infection in th spread of HIV and implications for tranmission prevention strategies in Lilongwe, Malawi: a modelling study. Lancet 2011;378.
101. Newsum AM, Ho CKY, Lieveld FI, et al. The hepatitis C virus nonstructural protein 3 Q80K polymorphism is frequently detected and transmitted among HIV-infected MSM in the Netherlands. AIDS 2017;31:105-12.
102. Franco S, Tural C, Nevot M, et al. Detection of a sexually transmitted hepatitis C virus protease inhibitor-resistance variant in a human immunodeficiency virus-infected homosexual man. Gastroenterology 2014;147:599-601 e1.
103. Degenhardt L, Charlson F, Stanaway J, et al. Estimating the burden of disease attributable to injecting drug use as a risk factor for HIV, hepatitis C, and hepatitis B: findings from the Global Burden of Disease Study 2013. The Lancet Infectious Diseases;16:1385-98.

104. Walker J, al. e. Projected impact and pathways to success of the hepatitis C virus elimination program in Georgia, 2015–2020. EASL Conference 2017, April 19-23 2017, Amsterdam, The Netherlands, Oral abstract 2017.



Chapter 8

Summarizing discussion and future perspectives

Part A: Optimization of hepatitis C therapy in the era of DAA

The advent of direct-acting antivirals (DAA), with cure rates of the most recent regimens up to 95% and higher, has changed the field of hepatitis C virus (HCV) infection. HCV infection has now become a curable disease for almost all patients. In part A of this thesis concerns the optimization of HCV therapy in the era of DAA as therapy shortening can be a strategy to reduce costs and improve adherence.

HepNed-001 study

The first clinical trial of this thesis looked at the efficacy of 8 weeks of ledipasvir/sofosbuvir (LDP/SOF) in non-cirrhotic patients infected with HCV genotype 4 (Chapter 2). With this shortened regimen, 37 of 39 patients of the on-treatment population were successfully treated for the HCV present at baseline (95%; 95% C.I. 83-99%). Although the study was limited to 44 patients only and therefore precluded the conclusion of statistical non-inferiority compared to a conservative fixed 95% success rate (deducted from earlier HCV genotype 4 treatment studies[1,2]), this outcome remains very relevant.

First, the initial phase 2 study and the study which led to the FDA- and EMA-approval of LDP/SOF for HCV genotype 4 infections included respectively 21 and 44 patients, which gives an indication about the obtainable sample sizes in the field of DAA research for HCV genotype 4. In the NIAID Synergy trial[1] and the 1119 study[2], respectively 20 out of 21 patients (95%; 95% C.I. 76-100%) and 41 out of 44 patients (93%; 95% C.I. 81-99%) with HCV genotype 4 infection were successfully treated with 12 weeks of LDP/SOF. Second, HCV genotype 4 infections are more frequently seen in low and middle income countries[3], but large therapeutic clinical trials used to focus on genotype 1 HCV mono-infections in high income countries[4]. Being able to shorten treatment for HCV genotype 4 could improve the access to therapy, especially in countries with a high prevalence of HCV genotype 4 and in which the costs of therapy limits its use. In fact, in 2015, prices for 12 weeks of LDP/SOF were considered as globally unaffordable and a threat to the sustainability of health care systems in many countries, preventing large-scale provision of treatment[5]. Even in 2017, 16 European countries still had restrictions for DAA therapy in place, which was not consistent

with the EASL guidelines for HCV treatment applied at the time and probably driven by economic choices[6]. Third, this clinical trial confirms the results reported by Shiha et al. who studied the efficacy of 8 weeks LDP/SOF in Egyptian HCV genotype 4 non-cirrhotic mono-infected patients of whom 41 of 44 patients were successfully treated (SVR12 95%; 95% C.I. 84-99%)[7]. Different from this Egyptian study, the HEPNED-001 study was the first to examine the efficacy of an 8-week regimen in patients with HCV genotype 4 regardless of their HIV status.

In addition to the difference in HIV-status compared to the study by Shiha et al., Dutch and Belgian HCV genotype 4 subtypes are different from the subtypes found in Egyptian genotype 4 patients. In Dutch genotype 4 patients, the (former) HCV epidemic among PWID and the current HCV epidemic in MSM consists mostly of HCV genotype 4d infections[8], but the Egyptian nosocomial epidemic consists mostly of HCV genotype 4a infections[9]. Although it has become clear that for the genotype 1 subtypes 1a and 1b treatment response can be different, this was initially less clear for the genotype 4 subtypes given the small number of HCV genotype 4 patients in clinical trials. However, recent studies seem to indicate that also for HCV genotype 4 not all subtypes seem to have the susceptibility for DAA therapy.

In the 1119-study, discussed earlier in this paragraph, SVR12 rates after 12 weeks of LDP/SOF were 100% for al subtypes except for genotype 4b (1 patient with the double NS5A RAS L28M + L31M) and 4r (2 patients with both L28M/V + L30R + L31M). However, all patients (n=44) had at least one baseline NS5A RAS, 21 patients had 2 NS5A RAS and 6 patients had 3 NS5A RAS, making the clinical interpretation difficult[2,10]. On the other hand, a French study which included 121 genotype 4 patients with virological failure after DAA treatment saw an over-representation of genotype 4r patients (n=27; 22%) compared to the prevalence in the general French population[11] and a Rwandan clinical trial found that after treatment with 12 weeks of ledipasvir/sofosbuvir only 54% of genotype 4r reached SVR12 compared to 87-100% for the other genotype 4 subtypes[12]. Furthermore, Welzel et al. analyzed 309 patients infected with HCV genotype 4 from several phase II/III DAA clinical trials[13]. The patients showed a wide range of HCV genotype 4 subtypes. Up to 11 different genotype 4 subtypes are circulating in Europe. This contrasts with HCV genotype 1 and 3, of whom mostly 1 or 2 subtypes circulate regionally. Interestingly, the level of baseline RAS

seemed to be subtype specific and especially genotype 4r harbored double or triple NS5A RAS at baseline. Reflecting the current African and Asian immigration to Europe, the proportion of patients with a non-4a/4d HCV may increase in the future[14].

In the HepNed-001 study, one of the patients with virological failure was infected with a HCV genotype 4c. In the other patient, an African migrant, the virus was non-typable but showed some similarities with both subtypes 4g and 4r. For future (research) purposes, it could be recommended to not only determine the HCV genotype with a reverse hybridizing assay (Versant® HCV Genotype 2.0 System; INNO-LiPA), but also determine the subtype in genotype 4 patients with for example NS5B sequencing[13] to at least monitor the local prevalence of RAS and the prevalence of the more difficult to treat HCV genotype 4 subtypes, like 4b and 4r.

In conclusion, the HepNed-001 study showed that a shortened 8 week regimen of LPD/SOF for non-cirrhotic HCV genotype 4 infected patients with a HCV RNA load <10 million IU/ml led to sustained virological response in 95% patients. This knowledge may facilitate the reduction of therapy costs, one of the WHO's priority actions regarding to the elimination of HCV infection as a public health by 2030. However, caution is advised with regard to non-4a/4d subtypes as discussed above. This stresses the importance of fully understanding the local HCV epidemic and tailoring interventions accordingly.

DAHHS 2 study

In the second clinical trial described in this thesis, concerns the efficacy of 8 weeks of grazoprevir/elbasvir (G/E) for the treatment of acute HCV infection (Chapter 3). In this multicenter single arm open label clinical trial, 79 out of 80 patients in the intention to treat population reached sustained virological response (99%; 95% C.I. 93-100%). Until recently, it was not known whether DAA treatment in the acute phase of HCV infection would be effective compared with their use for the treatment of chronic HCV infection. However, over the last few years the results of several studies on the use of DAA for the treatment of acute HCV infection became available. Nonetheless, they were all limited to small studies and most included only genotype 1 infected patients. This study is the first adequately powered clinical trial for the treatment of acute HCV infection with DAA to demonstrate

non-inferiority when compared to the cure rates observed with treatment of chronic HCV infection with the same regimen. The DAHHS 2 study proved that: 1) treatment of HCV infection with G/E in the acute phase is effective; 2) that the treatment duration can be shortened from 12-16 weeks to 8 weeks without loss of this effectiveness, and: 3) that in the Dutch setting of HIV-care treatment of acute HCV infection is feasible. The study in -and exclusion criteria required that patients initiated therapy within 26 weeks after infection and almost all patients could be treated within this timeframe.

At this moment, more clinical trials on the use of DAA for the treatment of acute HCV infection are ongoing. For glecaprevir/pibrentasvir (G/P), two small arms are added to the target3D-study in which 2 groups of 30 participants will be treated with either 6 weeks or 4 weeks of G/P (NCT02634008). And in the adequately powered REACT-study, 250 participants will be randomized 1:1 to 6 or 12 weeks of sofosbuvir/velpativir (SOF/VEL) (NCT02625909). The advantage of these regimens is their pan-genotypic nature which could allow for immediate treatment without genotype testing if proven to be effective for acute HCV infection of the genotype 3, as in regions were acute HCV infection is more often diagnosed in people who inject drugs, genotype 3 needs to be taken into account as well.

Part B: Effect of DAA and PrEP on the HCV epidemic among MSM

In **part B** of this thesis describes the effect of HCV direct-acting antivirals and HIV pre-exposure prophylaxis on the HCV epidemic among HIV-positive men who have sex with men. It takes the effects of two other recent developments into account: the unrestricted availability of direct-acting antivirals for chronic HCV infection (**Chapter 4 and 5**) and the introduction of HIV pre-exposure prophylaxis for HIV-negative persons at risk (**Chapter 6**). But first, to fully appreciate the HCV epidemic among these patients, the HCV care continuum is visualized in a schematic way as an extension to the treatment cascade discussed in **Chapter 4**.

Extension of the HCV 'treatment cascade' into a HCV 'care continuum'

To define which interventions may have a profound impact on the continuum of HCV care in a specific country or for a specific key population, it is important to understand the HCV epidemic. For HIV care, treatment cascades are widely used and global treatment goals are monitored with it (like the UNAIDS 90-90-90 HIV treatment targets). The advantage of such a visualization of the local epidemic is that 'gaps in care' are seen at a glance, as for every next step in the cascade a proportion of patients will be lost (as described in **Chapter 4**). However, the treatment cascade described in **Chapter 4** is merely a cross-sectional static representation of 'known' Dutch co-infected patients in care. To really understand and visualize the HCV epidemic among these patients one should look at the total HCV care continuum, which is more dynamic and also depends more on estimates than the treatment cascade (figure 1, next page). On left of the treatment cascade (in the dotted box) the following should be added: 1) the total population at risk for HCV infection and 2) the patients of whom the HCV status is unknown or patients who got lost to follow up (which together with the HCV/HIV-coinfected MSM tested and in care form an estimate for the 'true prevalence'). Neither does the HCV care continuum end with 'cure' (sustained virological response) as reinfections are frequently observed in certain high risk populations, and in particular, in HIV-positive MSM in the Netherlands[15,16]. Several aspects of the HCV care continuum will be discussed in greater detail in the next paragraphs with a specific focus on the impact of highly effective DAA.

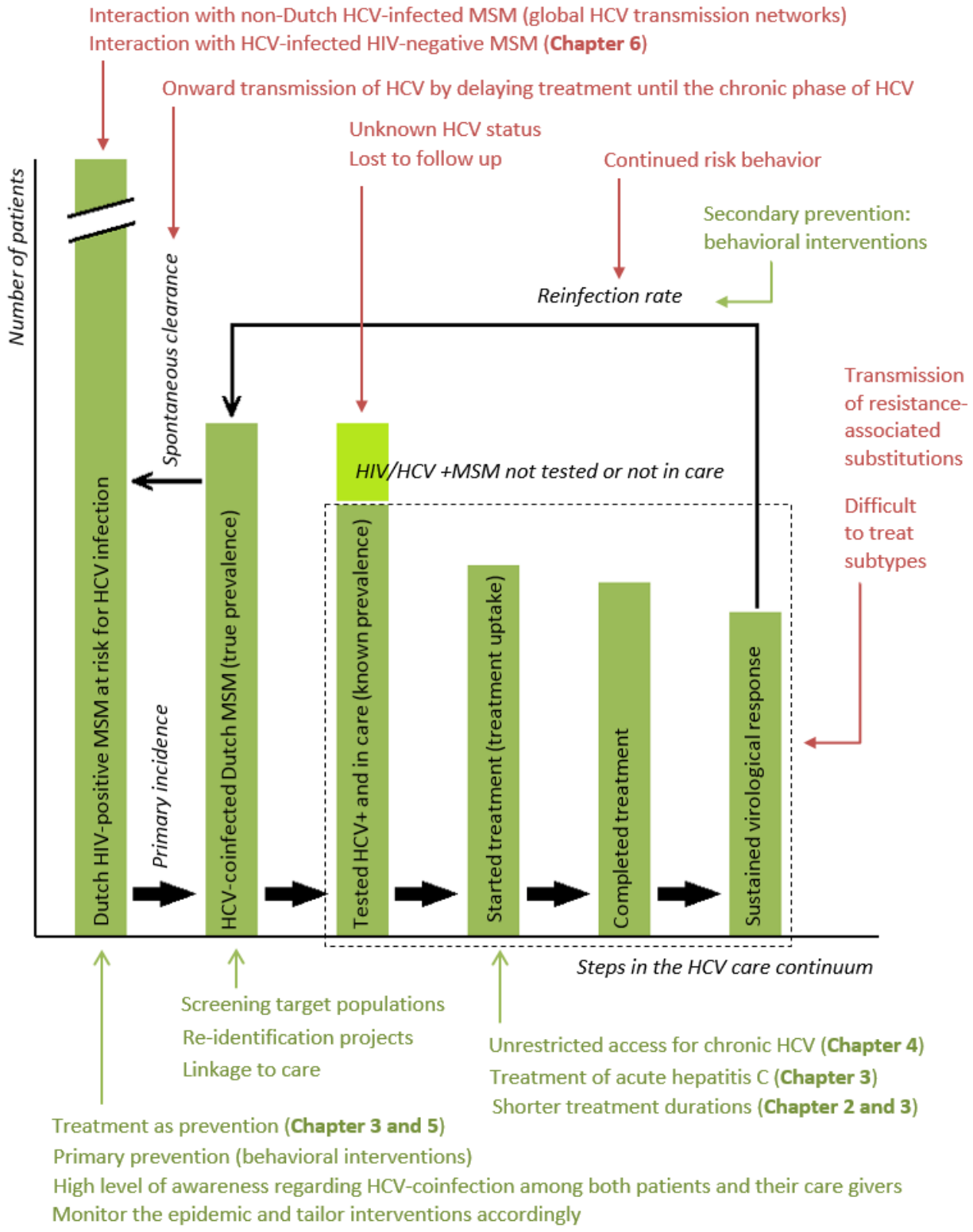


Figure 1. Schematic representation of the HCV continuum of care in Dutch HIV-positive MSM.

This continuum of care is depicted as an extended version of the treatment cascade discussed in Chapter 4 (in dotted box) as described on page 149. Possible barriers (in red) and strategies (in green) for HCV elimination among this key population are depicted around the HCV continuum of care and will be discussed separately throughout the summarizing discussion (this Chapter).

The effect of DAA on the HCV epidemic among Dutch HIV-positive MSM

1. The effect of unrestricted availability of DAA on the HCV prevalence

In Chapter 4 of this thesis describes the treatment cascade of the national HCV epidemic in HIV-positive patients up until February 2017 using data from the Dutch ATHENA cohort. This cohort captures data on 98% of patients with HIV in care in the Netherlands and is therefore highly representative of the overall Dutch HIV/HCV epidemic. The treatment uptake and treatment success of direct-acting antiviral therapy was investigated in the Dutch HIV-positive population shortly after the introduction and reimbursement of HCV direct-antiviral therapy. It showed that as of February 1st 2017, 76% of the Dutch HIV/HCV-coinfected patients in care had been successfully treated for HCV infection. A recent updated analysis of the cohort up until the 1ste of January 2018 showed that the number successfully patients increased to 83%[17]. Shortly after the study each HIV treatment center was provided with a coded list of patients remaining in need of curative HCV treatment in order to facilitate the identification and re-evaluation of these patients.

Treatment uptake and HCV cure rates were highest in MSM and significantly higher than in other categories of co-infected patients. Lifting the reimbursement restrictions, making DAA available for all patients regardless of fibrosis stage was followed by a major decline in HCV prevalence in HIV-positive MSM. However, practitioners should keep in mind that other HCV-infected populations, like PWID, non-Dutch patients and females, as described in Chapter 4, may need more support to (re-)start DAA therapy or during HCV therapy in order to avoid disparities in the national HCV treatment cascade.

2. The effect of unrestricted availability of DAA on the HCV incidence

Besides looking at the prevalence of chronic HCV infections among HIV-positive MSM, the incidence of HCV infections is of equal interest. In fact, one of the WHO's impact targets is a 90% reduction of new HCV cases by 2030. It is promising that treatment uptake is high among Dutch HIV-positive MSM which may favorably contribute to reduce ongoing HCV transmission in the Netherlands by interruption MSM-specific transmission networks[18-21]. Chapter 5 investigates the acute HCV incidence among Dutch HIV-positive men who have

sex with men before and after direct-acting antiviral therapies became available without restrictions in 2015. In 2016, there was a 51% decrease in acute HCV infections among Dutch HIV-positive MSM compared to 2014. This study was the first to describe empirical data in support of what recent modeling studies had predicted; universal HCV therapy for all HIV-positive MSM chronically infected with HCV will result in a decrease in the number of acute HCV infections in this population[22-24]. The high treatment uptake among Dutch HIV-positive MSM is the most likely explanation for the prompt decrease in HCV incidence among Dutch HIV-positive MSM, as high risk behavior is likely to be continued after HCV diagnosis, indicated by the high rate of STD's during this clinical trial and reported nationally for 2014 as well for 2016 by the RIVM.

However, this HCV treatment as prevention effect seen among Dutch HIV-positive MSM probably cannot be extrapolated to other key populations or even to other HCV epidemics among HIV-positive MSM due to different local settings. The type and extent of therapeutic interventions needed among HIV-positive MSM to reach the WHO's 2030 elimination targets seems to be dependent on the incidence trends and the local epidemical background (Chapter 7). Martin et al. showed that for the UK, with a stable HCV incidence (comparable to the situation within the Netherland before unrestricted access to DAA therapy), the elimination targets could be reached when treating all patients within 1 year after diagnosis or combining treatment scale up with behavioral risk reduction[25]. However, in the setting of increasing HCV incidences like observed in Switzerland and Berlin, modeling studies showed that despite treatment scale up the targets would not be reached and other intervention, like reduction in high-risk behavior, are definitely needed[23,26]. Moreover, Pradat et al. reported recently on an increasing primary HCV incidence in French HIV-positive MSM despite a high DAA uptake among the same high risk group[27]. Probably, the stable incidence rates and the very rapid DAA treatment uptake immediately after the lifted restriction criteria among Dutch HIV-positive MSM have been favorable factors the led to the incidence decline described in Chapter 5. However, Salazar-Vizcaya et al. predicted that although an intensive intervention (1 year of early DAA therapy combined with behavioral counseling) could lower the incidence over the intervention period, the benefit would disappear again over time after stopping the intervention[28], emphasizing the importance of continued efforts to tackle the epidemic.

3. The effect of DAA treatment for the acute phase of HCV infection

As stated for the HepNed-001 study (Chapter 2), shortening of therapy leads to a reduction of costs, which then could improve access to therapy. But when combining therapy shortening with treatment in the *acute* phase of HCV infection (Chapter 3), this could lead to a second and maybe equally important advantage in combating the HCV epidemic in high risk patients: treatment as prevention. Waiting for spontaneous clearance to avoid over-treatment of an infection seems sensible. Actually, the burden of disease after HCV acquisition only becomes apparent decades after infection and only in a subset of patients. Furthermore, treatment is expensive. However, when looking from a public health perspective, decreasing the time that a patient remains infectious after HCV acquisition and therefore treating patients as soon as possible after diagnosis makes sense as well: prevention of new infections in others could be an additional benefit of treatment of acute HCV infection. Moreover, 'HCV treatment as prevention (TasP)' could be even more effective than 'HIV TasP'[29], because HCV treatment has to be administered for months rather than a lifetime as in the case of HIV infection.

The current European guidelines on HCV treatment (EASL Recommendations on Treatment of Hepatitis C 2018[30] and European Guidelines for treatment of HIV-positive adults in Europe 2018 version 9.1[31] already advocate treatment of acute HCV infection 'without delay' and 'at diagnosis' if there is a high risk of onward transmission. However, these recommendations are based on expert-opinion, as at the time of writing of these guidelines, the ideal time point for starting treatment was not well-established and the impact on the epidemic and the cost-effectiveness of these interventions were largely unknown. Recently, two studies on the cost-effectiveness of immediate DAA therapy showed that this strategy could be cost-saving in the setting of risk of onwards transmission of HCV to others. Moreover, one of these studies was modelled in the setting of Dutch HIV-positive MSM.

Bethea et al. predicted that in the setting of patients at risk of transmitting HCV in the population with acute HCV infections in the United States, a shorted treatment of 6 instead of 8 weeks of LDP/SOF could be cost-saving[32]. For the Dutch situation, Popping et al. predicted that immediate DAA treatment at the cost of 35.000 euro per patient would both

lower the prevalence and incidence of HCV in HIV-positive MSM over the course of 40 years and that this strategy would be the most cost-saving, compared to waiting for spontaneous clearance (waiting 6 months until HCV infection becomes chronic) or deferring treatment to F2 stage fibrosis[33]. Sensitivity analysis showed that immediate treatment remained cost-saving, despite the fact that varying the DAA price between 5.000-50.000 euro had a substantial impact on the exact incremental cost-effectiveness ratio's (ICER). In the study, the authors did not take into account that in the setting of immediate treatment, treatment durations can be shortened compared to treatment of HCV in the chronic phase to save costs. However, at the time that the study by Popping et al. was performed, the exact costs of DAA therapy in the Netherlands were unknown as a result of price negotiations between companies and the ministry of health which remained undisclosed. However, in 2019 these negotiated deals came to an end and the acquisition costs of each of the DAA is now publicly available (table 1).

Table 1. Price of DAA combinations in the Netherlands.

Regimen	**Price for 12 weeks of treatment (€)***
Sofosbuvir	29.250
Ledipasvir/sofosbuvir	37.125
Paritaprevir/Ritonavir/Ombitasvir +/- Dasabuvir	35.408 +/- 3.152
Grazoprevir/Elbasvir	21.000
Glecaprevir/Pibrentasvir	36.000
Velpatasvir/Sofosbuvir	24.750
Velpatasvir/Sofosbuvir/Voxilaprevir	42.000

**Price in euro's for 12 weeks of treatment according to 'HCV richtsnoer' version 10 March 2019. Accessed at 17-04-2019, www.hcvrichtsnoer.nl.*

In summary, treatment of acute HCV infection with 8 weeks of G/E is a plausible strategy to bring us closer to the WHO 2030 elimination goals, at least in the setting of HIV-positive MSM. Immediate DAA therapy should be incorporated into Dutch treatment guidelines for Dutch HIV-positive MSM. It's effectivity in the acute phase of HCV infection has now been proven *and* the intervention is not only cost-effective but can even lead to costs saved if a shortened treatment duration can be prescribed as demonstrated in the DAHHS2 study. Furthermore, declining treatment for acute HCV infection in high risk patients because of the fear of swift reinfection can lead to stigma. This should be avoided at all costs to assure equal access to testing services and therapy.

Studies must be done in order to examine the feasibility of acute HCV therapy in other settings and for other DAA regimens. A major limitation for this treatment strategy is that, as acute HCV infection often is a subclinical disease, patients must be in a system where they can be frequently monitored for new HCV infections. For Dutch HIV-positive MSM, of whom most are in care and visit the HIV outpatient clinic regularly, this should not be a problem. However, this strategy might not be easily extrapolated to other settings in which monitoring of new infections and follow up of patients can be more chaotic (e.g. in PWID).

HCV infection among HIV-negative MSM in the PrEP era

Chapter 6 describes 10 cases of newly acquired HCV infections in Dutch and Belgian HIV-uninfected MSM that were encountered during the DAHHS 2 study. This case series illustrates that, even without an active HCV screening policy for HIV-negative MSM, acute HCV infections are diagnosed within this group. Until recently, sexually acquired HCV infections were regarded as limited to HIV-positive MSM as several cohort studies showed a low prevalence in HIV-negative MSM[34-36]. However, this case series shows that at least a subgroup of HIV-negative MSM are at increased risk and touches upon an important point in the discussion about HCV elimination in MSM: HIV pre-exposure prophylaxis (PrEP). In this case series, 5 out of the 10 patients were using PrEP and 1 patient used post-exposure prophylaxis on a very regular basis. Furthermore, all patients reported unprotected anal intercourse and most reported the use of oral drugs to increase sexual pleasure during intercourse (Chemsex). Therefore, the patients from this case series whom were not on

PrEP would actually have been good candidates to be prescribed PrEP and can be expected to start using PrEP as soon as it becomes available in the Netherlands. These results contrast with a recent study on the prevalence of anti-HCV antibodies at a large STI clinic in Amsterdam[37]. During October 2016 the anti-HCV prevalence among HIV-negative MSM was 1.0% as out of 504 HIV-negative MSM only 5 were anti-HCV positive and all were HCV RNA negative. The authors concluded that the HCV prevalence among HIV-negative MSM remained stable compared to previous years. However, this might not be true for the subgroup of HIV-negative MSM with the highest risk behavior. At the time of this HCV study at the STI clinic the AmPrEP study was already ongoing. In this PrEP demonstration project MSM receive PrEP and 3-monthly STI screening. Therefore, these "high-risk" MSM from Amsterdam were very likely to no longer attend the STI clinic. The HCV prevalence in these 375 PrEP-using MSM was 4.8% (95% C.I. 2.9-7.55)[38]. In another PrEP study, the London PROUD study, the analysis of the deferral arm showed that the study attracted population with higher STI rates than the general MSM population attending sexual health clinics in England[39]. These observations clearly illustrate that in specific MSM subgroups, like PrEP users, HCV monitoring is crucial. If other subgroups of MSM (e.g. MSM diagnosed with a STI) need to be monitored for HCV infection remains to be defined.

During the first PrEP clinical trials, the iPrEx and the PROUD study for continuous PrEP[40,41] and the ANRS IPERGAY trial analysis on demand PrEP[42], no compensatory increased sexual risk behavior was observed in MSM using PrEP. However, in the subsequent open-label phase of the ANRS IPERGAY trial, a significant decrease in condom use was seen[43]. Furthermore, among 220 MSM attending a sexual health clinic in Seattle and starting PrEP between 2014-2016, a decreased in condom use was reported as well[44]. These results were confirmed by recent results of the Dutch AmPrEP study as during the first 6 months after initiation of PrEP a significant increase in unprotected anal intercourse was observed[45]. The observations described above and the fact the use of PrEP may also reduce HIV-serosorting (the preferential selection of sex-partners with the same HIV serostatus) in the MSM community raises the question if the HCV prevalence in HIV-uninfected MSM will increase in the future as well. If so, could this hamper the future elimination of HCV among all MSM?

Several studies have already shown that sexual HCV transmission networks between HIV-positive and HIV-negative MSM are overlapping. In France, the HCV strains of 6 HIV-negative MSM (of whom 4 used PrEP) were included in different clusters of HCV-infected HIV-positive MSM[46]. In the Netherlands, 13 out of the 15 HIV-negative MSM with HCV RNA positivity in the AmPrEP study were part of 6 HIV-positive MSM-specific clusters. Thus the spread of HCV between HIV-negative and HIV-positive MSM is possible. However, studies have shown that HIV-negative patients do have a higher rate of spontaneous clearance. Thus as a larger part of these patients will not develop chronic disease and they have a considerably shorter period of being infectious to others, compared to HIV-positive MSM, the force of infection for this HIV-negative subgroup will be much lower. To date it is not clear whether transmission of HCV to HIV-negative MSM will hamper the future elimination of HCV in both HIV-negative and HIV-positive MSM.

However, as the care for HIV-negative MSM is divided between multiple care givers, like general practitioner and sexual health clinics, PrEP and STD tests can be easily ordered without medical surveillance (e.g. ordered online) and the number of HIV-negative MSM *at risk* is not clear, surveillance of the HCV incidence and prevalence may become very difficult within the next few years. Furthermore, monitoring the incidence of HCV among risk-groups is difficult and can at times be unreliable was recently illustrated in a study on the incidence of acute HCV among HIV-positive MSM in the Netherlands. In this study, incident acute HCV infections were prospectively registered in 19 HIV clinics spread across the Netherlands[47]. This observed number was much higher compared to the national number of acute HCV infections reported by the RIVM[48], despite the fact that it is obligatory to report an acute HCV infection. To prevent this from happening for HIV-negative MSM, different stake holders (general practitioners, sexual health clinics, hepatologists, infectiologists, etc.) have to cooperate. At least nationwide surveillance, specifically designed to monitor acute HCV infections, should be in place to keep track of the periodic HCV incidence among this risk group. This is currently not the case because STD clinics in the Netherlands do not test HIV-negative MSM for HCV infection in a systematic way and a system to periodically monitor HIV-negative MSM is not in place. With the expected roll-out of PrEP at GGD clinics across the Netherlands, monitoring for HCV infection among HIV-negative PrEP users should become feasible on short notice.

Part C: Is micro-elimination of HCV in Dutch HIV-positive MSM possible?

Final summary and implications for future research

The overall aim of this thesis was to investigate and discuss possible barriers and strategies for micro-elimination of HCV infection among Dutch HIV-positive MSM in the era of DAA.

In order to be able to eliminate an infectious disease, the following biological criteria need to be present: 1) the availability of an effective intervention and the possibility to implement it; 2) the availability of a diagnostic tool with sufficient sensitivity and specificity, and; 3) humans are essential for the life cycle of the agent and the only reservoir for the infectious disease[49]. And, in fact, only two actions are needed to eliminate an infectious disease: existing infections must be found and cured (lowering the prevalence, chapter 4); plus new infections must be prevented (lowering the incidence; chapter 5). However, the path towards elimination consist of many small intertwined steps as will be discussed in this final part. Moreover, the financial, social and political commitment to (future) elimination plans play a big role[49]. Fortunately, the WHO has created this commitment by releasing the 2030 elimination goals for viral hepatitis. As discussed in the introduction (Chapter 1), one of these WHO's 2030 elimination goals consists of a 90% drop in HCV incidence to establish elimination of HCV as a public health threat and to reassure 'control' of the HCV epidemic at locally acceptable level[49,50]. The WHO stated that the continuum of HCV care should be tailored to the specific epidemic within a population or setting to curb the epidemic in order to reach these elimination goals. Micro-elimination, which can be defined as 'reaching the WHO 2030 targets within a local well-defined key population', is often regarded as more feasible than national or global elimination as specific interventions can be implemented faster and more efficiently within a specific key population[51].

This thesis specifically looks at interventions regarding the HCV epidemic among HIV-positive MSM as they are a well-defined population in the Netherlands. Although it will never be possible to discuss all the factors influencing an epidemic, this last paragraph sums up the most relevant factors contributing to or hampering the WHO's 2030 elimination goals for HCV infection among Dutch HIV-positive MSM (Figure 1, page 151) and assess the implications for future research.

Barriers that could hamper the WHO elimination goals among Dutch HIV-positive MSM

1. Interaction with HCV-infected HIV-negative MSM, as describe in more detail in Chapter 6 and this previous paragraph of this summarizing discussion, could hamper the elimination of HCV infection among both HIV-negative and HIV-positive MSM. Ideally, a nationwide database, with a known total number HIV-negative MSM (denominator), should be in place to precisely monitor the HCV incidence within this subgroup. At this moment, a database of HCV-monoinfected patients is being developed[52]. Furthermore, in the near future an large epidemiological study will be executed across STD clinics in the Netherlands and Belgium to give a reliable estimate of the HCV prevalence among HIV-negative MSM.

2. As the Dutch MSM network is not a closed system, interaction with non-Dutch HCV-infected MSM within global transmission networks could hamper the elimination of HCV. In 2009, van de Laar et al. revealed a large international network of HCV transmission among HIV-positive MSM with phylogenetic analysis[20]. However, a recent study showed that for the Swiss situation, although both international and domestic HCV transmission have played major roles in their epidemic between 2000 and 2007, local HCV transmission among HIV-positive MSM was the main source of infection between 2008 and 2016[21]. Future studies should access to which extent global and European interaction between MSM could influence the local Dutch HCV epidemic. And if so, efforts should be made to eliminate HCV among HIV-positive MSM on an European and maybe even global level.

3. Recently, 4 local retrieval projects for once HCV-positive patients whom are lost to follow up were executed[52]. For Dutch HIV-positive MSM re-identification seems less relevant, as there are regarded as a subgroup with a high linkage to care and with a small proportion of undiagnosed patients. Kracht et al. found that after analyzing 269 'lost to follow-up'-patients with a positive HCV test between 2001 and 2015, 42 patients chronic HCV infections were re-identified. However, in only one of these patients HCV infection could be attributed to unsafe sexual activities, as most patients were infected through (former) IVDU (76%)[53]. However, within the Swiss HCVree trial,

screening of 3722 of 4257 HIV-positive MSM for HCV RNA between October 2015 and May 2016, revealed 177 patients with an undiagnosed ongoing HCV infection of whom 24 had an acute HCV infection[54]. Furthermore, a Dutch modelling study showed that an increased frequency of screening with HCV PCR, targeted at a group of previously infected patients and in combination with immediate DAA therapy, could positively affect the HCV epidemic among HIV-positive MSM in a cost-effective way[55]. Future studies should look at inventive ways to diagnose HCV infections early in high-risk MSM.

4. The high reinfection rate among HIV-positive MSM is a major problem[16,56]. The reinfection rate (secondary incidence) is higher than the primary incidence (Chapter 7). Besides raising awareness among the total HIV-positive MSM population (primary prevention), behavioral interventions should be specifically targeted at HCV-infected HIV-positive MSM (secondary prevention). Modeling showed that behavioral interventions can have a large impact on the prevalence and incidence of HCV among the HIV positive MSM population[23]. For HIV infection, a Cochrane review and meta-analysis, in which 40 studies on behavioral interventions regarding sexual risk behavior among HIV-negative MSM were analyzed, showed that behavioral interventions in this group can lead to a significant reduction in number of partners and/or a reduction in unprotected anal sex[57]. However, it is not known whether these interventions will be as effective in HIV-positive MSM. A recent qualitative study among 20 Dutch HIV-infected MSM showed that a low level of perceived self-efficacy (an individual's belief in their innate ability to achieve goals) was a prominent barrier to behavioral change and that this was directly influenced by drug-use (Chemsex). More research should be focused on behavioral change in MSM at risk for HCV reinfection.

5. DAA are quite expensive and therefore under mining the sustainability of health care systems. Although Popping et al. showed that acute DAA therapy could be cost-effective in the setting of Dutch HIV-positive MSM, this does not mean that the 3 or 5-year budget impact is affordable within our healthcare system. For the Netherlands, there is no maximal affordability threshold. The affordability of costly drugs is improved through price negations and price/volume arrangements with the pharmaceutical industry until the budget impact and ICER are acceptable (with a cost-effectiveness

threshold of 80.000/QALY)[58]. As spontaneous clearance among HIV-positive MSM is low, most acutely infected men will continue to be treated for chronic HCV infection. Expanding reimbursement criteria for acute HCV infection for this subgroup will probably not lead to unaffordable rise of the budget impact of this intervention, thus its implementation should be on the political agenda. Nonetheless, the high costs of DAA's and their budget impact are still a global concern as it forbids equal access to therapy, especially in middle and low income countries, even after voluntary licencing[59].

6. Although resistance-associated substitions (RAS) did not play a major role in the clinical trials in this thesis (Chapter 2 and chapter 3), Newsum et al. showed that both the NS3 Q80K polymorphism and the NS5B S282T RAS, resp. associated with simeprevir and sofosbuvir resistance, were found in Dutch MSM-specific clusters[19,60]. As discussed in Chapter 4, RAS prevalence can be subtype or key population specific. Efforts should be undertaken to systematically monitor RAS frequencies within initiatives like HEPCARE (an European HCV program to monitor resistance to direct-acting antiviral agents in real life[61]) in an attempt to, in the case of newly emergent RAS with high resistance to therapy, adjust treatment accordingly before they possibly becomes widespread.

Factors that (can) positively influence HCV elimination among Dutch HIV-positive MSM

1. The HCV care continuum among HIV-positive MSM is interwoven with already existing and well-developed HIV care continuum. Therefore, HCV care for HIV-positive MSM is nationally organized and monitored with tight collaboration between various partners. Dutch HIV-positive MSM are regularly and systematically screened for HCV infection as specified in the national HIV guideline (as described in Chapter 1), and, national data on HCV infections in this subgroup is collected through the already existing ATHENA-cohort (Chapter 4). This makes thigh monitoring of the HCV epidemic among Dutch HIV-positive MSM feasible, thereby making it possible to assess the possible effects of other epidemiological coinciding trends. Also patient advocacy organizations are nationally well-organized, thereby partnering in raising patient awareness and actively involved in implementation of new interventions.

2. This thesis describes that DAA therapy can positively impact the HCV-epidemic among HIV-positive MSM. High treatment uptake after unrestricted access to DAA therapy for chronically infected MSM led to a decline in prevalence and incidence in this key population (treatment as prevention; Chapter 4 and 5).

3. Treatment of acute HCV infection is effective, feasible and cost-effective in the setting of Dutch HIV-positive MSM and should be implemented to further exploit the treatment as prevention effect within this population (Chapter 3).

4. Treatment shortening of LDP/SOF is not only possible for genotype 1. It is also possible for but also for genotype 4 infected patients (without liver cirrhosis and a viral load < 10 million IU/mL) (Chapter 2). This is important as genotype 4 is the second most prevalent genotype among Dutch HIV-positive MSM and as it could reduce costs and possibly improve adherence.

Although some of these factors cannot be applied to other key populations or might not be effective in other settings, they seem to work for Dutch HIV-positive MSM and future research should focus on their possible effects in different key populations or different local settings.

References

1. Kohli A, Kapoor R, Sims Z, et al. Ledipasvir and sofosbuvir for hepatitis C genotype 4: a proof-of-concept, single-centre, open-label phase 2a cohort study. Lancet Infect Dis 2015;15:1049-54.
2. Abergel A. MS, Samuel D., Jiang D., Kersey K., Pang P. S., Svarovskaia E., Knox S. J., Loustaud-Ratti V., Asselah T. Ledipasvir plus sofosbuvir for 12 weeks in patients with hepatitis C genotype 4 infection. Hepatology 2016;64:1049-56.
3. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 2015;61:77-87.
4. Asselah T, Hassanein T, Waked I, Mansouri A, Dusheiko G, Gane E. Eliminating hepatitis C within low-income countries - The need to cure genotypes 4, 5, 6. J Hepatol 2017.
5. Iyengar S. TTK, Vogler S., Beyer P., Wiktor S., de Joncheere K., Hill S.,. Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis. PLoS Med 2016;13:e1002032.
6. Marshall AD, Cunningham EB, Nielsen S, et al. Restrictions for reimbursement of interferon-free direct-acting antiviral drugs for HCV infection in Europe. Lancet Gastroenterol Hepatol 2018;3:125-33.
7. Shiha G, Esmat G, Hassany M, et al. Ledipasvir/sofosbuvir with or without ribavirin for 8 or 12 weeks for the treatment of HCV genotype 4 infection: results from a randomised phase III study in Egypt. Gut 2018.
8. de Bruijne J, Schinkel J, Prins M, et al. Emergence of hepatitis C virus genotype 4: phylogenetic analysis reveals three distinct epidemiological profiles. J Clin Microbiol 2009;47:3832-8.
9. Frank C, Mohamed MK, Strickland GT, et al. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. Lancet 2000;355:887-91.
10. Camus G, Han B, Asselah T, et al. Resistance characterization of ledipasvir and velpatasvir in hepatitis C virus genotype 4. J Viral Hepat 2018;25:134-43.
11. Fourati S, Rodriguez C, Hezode C, et al. Frequent antiviral treatment failures in patients infected with hepatitis C virus genotype 4, subtype 4r. Hepatology 2018.
12. Gupta N, JK, CM, et al. Direct-acting antiviral treatment in sub-Saharan Africa: A prospective trial of Ledipasvir/Sofosbuvir for chronic Hepatitis C infection in Rwanda (the SHARED study). April 2018Volume 68, Supplement 1, Page S50
13. Welzel TM, Bhardwaj N, Hedskog C, et al. Global epidemiology of HCV subtypes and resistance-associated substitutions evaluated by sequencing-based subtype analyses. J Hepatol 2017;67:224-36.
14. Ngui SL, Brant L, Markov PV, et al. Hepatitis C virus genotype 4 in England: diversity and demographic associations. J Med Virol 2015;87:417-23.
15. Ingiliz P, Martin TC, Rodger A, et al. HCV reinfection incidence and spontaneous clearance rates in HIV-positive men who have sex with men in Western Europe. Journal of hepatology 2017;66:282-7.
16. van Sighem A.I. BTS, Wit F.W.N.M., Smit C., Matser A., Reiss P.,. Monitoring Report 2017. Human Immunodeficiency Virus (HIV) Infection in the Netherlands. . Stichting HIV Monitoring, 2017 Available online at wwwwhiv-monitoringnl.
17. C. Smit AB, A. Newsum, et al.,. HCV treatment cascade in the Netherlands: DAA uptake varies by key population, effectiveness of HIV treatment and co-medication use. AIDS2018, 26th of July, 2018, Amsterdam, abstract WEPEB082.
18. Vanhommerig JW, Bezemer D, Molenkamp R, et al. Limited overlap between phylogenetic HIV and hepatitis C virus clusters illustrates the dynamic sexual network structure of Dutch HIV-infected MSM. AIDS (London, England) 2017;31:2147-58.
19. Newsum AM, Ho CK, Lieveld FI, et al. The hepatitis C virus nonstructural protein 3 Q80K polymorphism is frequently detected and transmitted among HIV-infected MSM in the Netherlands. AIDS (London, England) 2017;31:105-12.
20. van de Laar T, Pybus O, Bruisten S, et al. Evidence of a large, international network of HCV transmission in HIV-positive men who have sex with men. Gastroenterology 2009;136:1609-17.

21. Salazar-Vizcaya L, Kouyos RD, Metzner KJ, et al. Changing trends in international versus domestic HCV transmission in HIV-positive MSM: A perspective for the DAA scale-up era. The Journal of infectious diseases 2019.
22. Hullegie SJ NB, Rijnders BJ, de Knegt RJ, Rockstroh JK, Boucher CA, van de Vijver DA. Is HCV Elimination Possible? A Modeling Study of HIV-Positive MSM. Oral presentation at CROI conference February 22–25, 2016 Boston, Massachusetts, abstract 536.
23. Salazar-Vizcaya L, Kouyos RD, Zahnd C, et al. Hepatitis C virus transmission among human immunodeficiency virus-infected men who have sex with men: Modeling the effect of behavioral and treatment interventions. Hepatology 2016;64:1856-69.
24. Martin NK, Thornton A, Hickman M, et al. Can Hepatitis C Virus (HCV) Direct-Acting Antiviral Treatment as Prevention Reverse the HCV Epidemic Among Men Who Have Sex With Men in the United Kingdom? Epidemiological and Modeling Insights. Clin Infect Dis 2016;62:1072-80.
25. Martin NK, Thornton A, Hickman M, et al. Can Hepatitis C Virus (HCV) Direct-Acting Antiviral Treatment as Prevention Reverse the HCV Epidemic Among Men Who Have Sex With Men in the United Kingdom? Epidemiological and Modeling Insights. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2016;62:1072-80.
26. Martin N JK, Boesecke C, et al. . Can HCV be eliminated among HIV-infected MSM in Berlin? Modeling a setting with increasing incidence and high treatment rates. American Association for the Study of Liver Diseases (AASLD), The Liver Conference 2017 Washington, DC 19-21 Oct 2017 2017.
27. Pradat P, Huleux T, Raffi F, et al. Incidence of new hepatitis C virus infection is still increasing in French MSM living with HIV. Aids 2018;32:1077-82.
28. Salazar-Vizcaya L, Kouyos RD, Fehr J, et al. On the potential of a short-term intensive intervention to interrupt HCV transmission in HIV-positive men who have sex with men: A mathematical modelling study. Journal of viral hepatitis 2018;25:10-8.
29. Yombi JC, Mertes H. Treatment as Prevention for HIV Infection: Current Data, Challenges, and Global Perspectives. AIDS reviews 2018;20:131-40.
30. EASL Recommendations on Treatment of Hepatitis C 2018. Journal of hepatology 2018;69:461-511.
31. European Guidelines for treatment of HIV-positive adults in Europe, version 9.1. http://wwweacsocietyorg/guidelines/eacs-guidelines/eacs-guidelineshtml.
32. Bethea ED, Chen Q, Hur C, Chung RT, Chhatwal J. Should we treat acute hepatitis C? A decision and cost-effectiveness analysis. Hepatology 2017.
33. Popping S, Hullegie SJ, Boerekamps A, et al. Early treatment of acute hepatitis C infection is cost-effective in HIV-infected men-who-have-sex-with-men. PLoS One 2019;14:e0210179.
34. Urbanus AT, Van De Laar TJ, Geskus R, et al. Trends in hepatitis C virus infections among MSM attending a sexually transmitted infection clinic; 1995-2010. AIDS (London, England) 2014;28:781-90.
35. Ghisla V, Scherrer AU, Nicca D, Braun DL, Fehr JS. Incidence of hepatitis C in HIV positive and negative men who have sex with men 2000-2016: a systematic review and meta-analysis. Infection 2016.
36. Yaphe S, Bozinoff N, Kyle R, Shivkumar S, Pai NP, Klein M. Incidence of acute hepatitis C virus infection among men who have sex with men with and without HIV infection: a systematic review. Sex Transm Infect 2012;88:558-64.
37. Newsum AM, van Rooijen MS, Kroone M, et al. Stable low hepatitis C virus antibody prevalence among HIV-negative MSM attending the STI outpatient clinic in Amsterdam, 2007 - 2017. Sex Transm Dis 2018.
38. Hoornenborg E, Achterbergh RCA, Schim Van Der Loeff MF, et al. Men who have sex with men starting pre-exposure prophylaxis (PrEP) are at risk of HCV infection: evidence from the Amsterdam PrEP study. Aids 2017.
39. Dolling DI, Desai M, McOwan A, et al. An analysis of baseline data from the PROUD study: an open-label randomised trial of pre-exposure prophylaxis. Trials 2016;17:163.
40. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med 2010;363:2587-99.

41. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet 2016;387:53-60.
42. Molina JM, Capitant C, Spire B, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. N Engl J Med 2015;373:2237-46.
43. Molina JM, Charreau I, Spire B, et al. Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. Lancet HIV 2017;4:e402-e10.
44. al. MMe. Changes in sexual behaviour and STI diagnoses among MSM using PrEP in Seattle, WA. Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 979, 2017.
45. Hoornenborg E, Coyer L, van Laarhoven A, et al. Change in sexual risk behaviour after 6 months of pre-exposure prophylaxis use: results from the Amsterdam pre-exposure prophylaxis demonstration project. Aids 2018;32:1527-32.
46. Charre C, Cotte L, Kramer R, et al. Hepatitis C virus spread from HIV-positive to HIV-negative men who have sex with men. PLoS One 2018;13:e0190340.
47. Hullegie SJ, van den Berk GE, Leyten EM, et al. Acute hepatitis C in the Netherlands: characteristics of the epidemic in 2014. Clin Microbiol Infect 2015.
48. A.A.M. van Oeffelen FvA, I.V.F. van den Broek, E.L.M. Op de Coul, P.J. Woestenberg, J.C.M. Heijne, C. den Daas, S.H.I. Hofstraat, A.I. van Sighem, M.M.J. Nielen, B.H.B. van Benthem. Sexually transmitted infections including HIV, in the Netherlands in 2014. Rijksinstituut voor Volksgezondheid en Milieu RIVM;26-Jun-2015
49. Dowdle WR. The principles of disease elimination and eradication. Bull World Health Organ 1998;76 Suppl 2:22-5.
50. WHO. Global health sector strategy on viral hepatitis 2016-2021, towards ending viral hepatitis. June 2016.
51. Lazarus JV, Wiktor S, Colombo M, Thursz M, Foundation EIL. Micro-elimination - A path to global elimination of hepatitis C. J Hepatol 2017;67:665-6.
52. Kracht PAM, Arends JE, van Erpecum KJ, et al. Strategies for achieving viral hepatitis C micro-elimination in the Netherlands. Hepatol Med Policy 2018;3:12.
53. Kracht PAM, Arends JE, van Erpecum KJ, et al. REtrieval And cure of Chronic Hepatitis C (REACH): Results of micro-elimination in the Utrecht province. Liver Int 2019;39:455-62.
54. Braun DL, Hampel B, Martin E, et al. High Number of Potential Transmitters Revealed in a Population-based Systematic Hepatitis C Virus RNA Screening Among Human Immunodeficiency Virus-infected Men Who Have Sex With Men. Clin Infect Dis 2019;68:561-8.
55. S. Popping BEN, J.J.A. van Kampen, A. Verbon, C.A.B. Boucher, D.A.M.C. van de Vijver. Intensive hepatitis C monitoring in previously HCV infected HIV-positive MSM is a cost saving method to reduce the HCV epidemic. Oral at NCHIV 2016, abstract number O10, http://nchivorg/abstracts/ 2016.
56. Ingiliz P, Martin TC, Rodger A, et al. HCV reinfection incidence and spontaneous clearance rates in HIV-positive men who have sex with men in Western Europe. J Hepatol 2017;66:282-7.
57. Johnson WD, Diaz RM, Flanders WD, et al. Behavioral interventions to reduce risk for sexual transmission of HIV among men who have sex with men. Cochrane Database Syst Rev 2008:CD001230.
58. Flume M, Bardou M, Capri S, et al. Approaches to manage 'affordability' of high budget impact medicines in key EU countries. J Mark Access Health Policy 2018;6:1478539.
59. Assefa Y, Hill PS, Ulikpan A, Williams OD. Access to medicines and hepatitis C in Africa: can tiered pricing and voluntary licencing assure universal access, health equity and fairness? Global Health 2017;13:73.
60. Newsum AM, Molenkamp R, van der Meer JT, et al. Persistence of NS5B-S282T, a sofosbuvir resistance-associated substitution, in a HIV/HCV-coinfected MSM with risk of onward transmission. J Hepatol 2018;69:968-70.
61. Popping S, Cento V, Garcia F, et al. The need for a European hepatitis C programme monitoring resistance to direct-acting antiviral agents in real life to eliminate hepatitis C. J Virus Erad 2018;4:179-81.