Changing perspectives

Hepatitis C virus infection in key populations

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Changing perspectives

Hepatitis C virus infection in key populations

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Chapter 1

Introduction and outline of thesis

1.1 Hepatitis C virus infection

Hepatitis C virus (HCV) infection is ominously known as 'the silent killer', since it can lead to liver inflammation, slowly causing cirrhosis, liver function failure and eventually possibly hepatocellular carcinoma, without the infected person being aware of it for years [1]. HCV is a blood-borne virus and was called non-A-non-B-hepatitis for several decades before the structure of the virus was recognized in 1989 [2], after which blood screening and limited treatment options became available. Thirty years later, the epidemic of HCV infection increasingly constitutes a major public health burden [3]. Only in recent years, the development and availability of new treatment options (direct-acting antivirals, DAA) are strengthening the hope to surmount this extensive health problem [4].

Virology, immunology and diagnostic methods

HCV is an enveloped, single-stranded RNA virus of the Flaviviridae family. The virus replicates primarily in the hepatocytes of the liver. As a result of a high rate of replication, and a lack of proofreading by the HCV RNA polymerase, it mutates rapidly. This causes so many variations that the virus is considered a quasispecies [5]. Based on genetic differences, the virus species is classified into eight genotypes [6] and more than a hundred subtypes [7]. It is possible to be infected with a second subtype during already existent infection. This is called superinfection [8].

The virus can be detected in blood by Polymerase Chain Reaction (PCR) 2-3 weeks after infection [9]. Serologic tests can detect anti-HCV antibodies on average after 4-10 weeks, and in 97% of monoinfected persons 6 months after exposure [10]. Delayed HCV antibody seroconversion has been observed in HIV-infected persons; in a study by Thomson et al. 37% of HIV-infected men who have sex with men (MSM) with acute HCV tested antibody negative 3 months after the first HCV RNA positive test and 10% still tested antibody negative 9 months after the first RNA positive test [11, 12]. Reliable, low-cost tests, that will preferably detect acute as well as chronic HCV infections, are needed since it is estimated that worldwide only 20% of HCV-infected persons is aware of being infected [3].

Transmission routes

Transmission of HCV occurs primarily through blood-to-blood contact. Several routes of exposure exist and the risk of infection depends in part on the application of hygienic prevention measures. Before the recognition of the virus, the most common transmission route was through medical procedures with contaminated equipment or products, specifically blood transfusions or organ transplants, injections with contaminated needles and syringes, and surgical or dental procedures [13]. In countries where blood products are routinely screened for HCV, and where sterilization of medical equipment and the use

of clean injection needles is standard, transmission of HCV in medical settings has declined dramatically [14]. However, in many low- or middle-income countries such prevention measures are non-existent or suboptimal.

Injecting drug use with shared contaminated injecting equipment is another route of transmission. It has been demonstrated that easily accessible harm reduction programmes, including needle and syringes exchange programmes and opiate substitution therapy, are associated with a reduced HCV incidence [15-18]. Still, these programmes are not available for many people who inject drugs (PWID) worldwide [19, 20].

The risk of vertical HCV transmission is estimated at 6% of children of HCV viraemic women, with an increase in risk to 10% when the mother is HIV coinfected and viraemic [21]. Treatment with antiretroviral therapy (ART) in coinfected women during pregnancy may reduce transmission risk of both viruses, though evidence is varying [22]. Sharing of contaminated household objects such as razors or tooth brushes poses another, but smaller risk [23].

Although the virus can be found in semen [24], the risk of sexual transmission among heterosexual stable serodiscordant couples is considered low [25]. However, among HIV-infected MSM, sexual contact is considered the main route of transmission in the current epidemic [26, 27], as we will discuss further below.

Worldwide epidemiology

In 2015, an estimated 71 million persons worldwide were living with chronic HCV [28]. Annually, approximately 1-2 million individuals are newly infected. Around 400.000 persons per year die due to complications of HCV infection (mainly cirrhosis and hepatocellular carcinoma) [3]. HCV has spread globally but prevalence and incidence differ widely per region (figure 1) and depend strongly on availability of prevention measures and treatment [29]. For example, in Egypt, the HCV antibody prevalence is still as high as 10% and HCV RNA prevalence 7%, as a result of population-wide unhygienic schistosomiasis vaccination campaigns from the 1920s until early 1980s [30, 31]. Other regions with a high prevalence of HCV are East and Central Sub-Saharan Africa, Eastern Europe, Russia and Central and Southeast Asia [32]. This has to do with ongoing epidemics of unhygienic injecting drug use, limited hygienic practice in medical care and relatively high HIV-coinfection rates. In contrast, in most high income countries the prevalence in the general population is as low as 0.5%-2% and mainly a consequence of popularity of injecting drug use in a subpopulation 40 years ago [33].

The current epidemic of sexually transmitted HCV among HIV-infected MSM started in several big cities in Europe, the USA and Australia in the mid-1990s but was first recognized after 2002 when it further expanded [34, 35]. This increase has also been reported in urban areas in Asia [36, 37]. Phylogenetic analysis can be used to study the evolutionary

relationship between genetic variants of the virus and to identify transmission networks. With this method it has been demonstrated that the transmission network of MSM is largely separate from that among PWID and internationally linked in a network in Europe [38]. In MSM, the most prevalent HCV genotypes are 1a and 4d and in PWID this differs per region, but genotype 1 is worldwide the most prevalent [39].

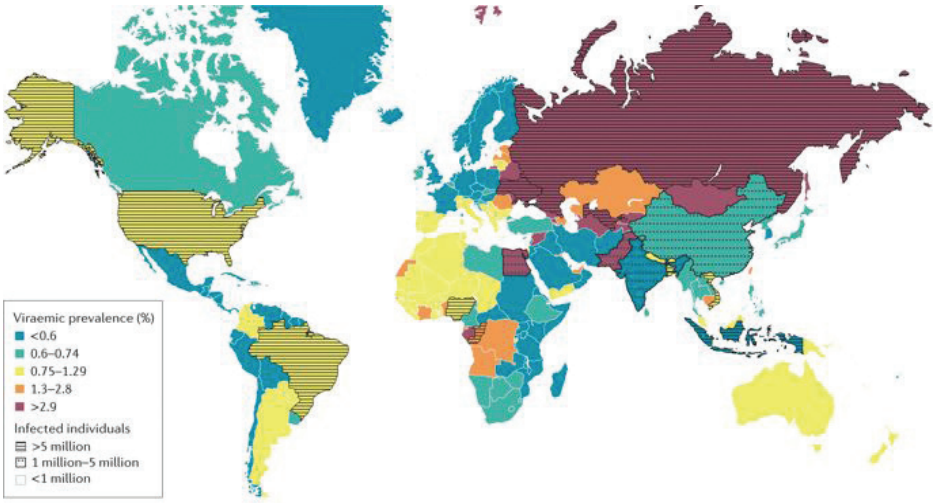

Figure 1. HCV prevalence. Schematic representation of the actual viraemic HCV prevalence and the extrapolated total HCV infections per country in 2015. Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Disease Primers, copyright 2017.

Natural course of disease

The incubation period of HCV ranges between 2 weeks and 6 months. Elevations of serum ALT levels are on average noticeable after 6 to 9 weeks. Infection is often clinically unnoticed since symptoms in the acute phase of infection are rare and consist of flu like symptoms (15-30%) with occasionally jaundice [40, 41]. Spontaneous clearance of the virus occurs and is defined as having two RNA negative test results with a time-interval of at least 24 weeks, without having had any treatment [42, 43]. About 25% of monoinfected persons are able to spontaneously clear the virus in the acute phase of infection [44]. Female sex, genotype 1 and IFNL3 genetic variant (previously known as IL28b) are associated with spontaneous clearance [42, 45]. After either spontaneous clearance or successful treatment it is possible to be reinfected (with the same and other genotypes) when re-exposure to HCV occurs [46]. Of persons who become chronically infected and remain untreated, 5-30% will develop complications over a period of 20-30 years, without noticing any symptoms in this long time period. At first, liver fibrosis develops, which can be graded from mild to severe according

to different histological scoring systems [47]. Next, chronic infection is complicated by liver cirrhosis, which will finally lead to loss of liver function; 16-41% of chronically infected persons will progress to cirrhosis depending on time followed since infection. Of patients with cirrhosis, 2-4% per year develop hepatocellular carcinoma and fulminant liver failure, leading to death [48]. Extrahepatic complications are arthralgia, fatigue, systemic diseases, vasculitis due to cryoglobulinemia, porphyria, hematological cancers, diabetes mellitus and depression [49].

HIV coinfection

Due to the shared transmission routes HCV infection is common in persons with HIV infection. A systematic review and meta-analysis in 2016 reported that of the approximately 37 million people affected with HIV, an estimated 2.3 million (6%) were also infected with HCV [50]. Coinfection is particularly prevalent among HIV-infected PWID (80-90%). HIV-HCV coinfection through sexual transmission is less common, except among the MSM population [26]. Sexually transmitted HCV infection is mostly confined to HIV-infected MSM. It is hypothesized that HIV infection increases the susceptibility for HCV infection through sexual transmission, despite treatment for HIV [51]. Moreover, high risk sexual behaviour and concurrent STI associated with HCV infection are more common among HIV-infected MSM compared to uninfected MSM and this may facilitate HCV transmission in this group [52, 53]. Clinically, there are several consequences of HIV coinfection. A delay in HCV seroconversion, as described in the paragraph on diagnostic methods, may lead to a delay in HCV diagnosis and treatment [11, 12]. Furthermore, existing HIV infection hampers clearance of subsequent HCV infection [54], leading to clearance rates of 11-15% compared to 25% in HCV monoinfected persons [55, 56].

Furthermore, HIV infection is associated with increase in HCV replication [57]. HIV also leads to faster deterioration of HCV-related liver disease, possibly even when HIV is effectively treated with ART [58, 59]. The other way around it is proposed that HCV contributes to HIV pathogenesis through immune exhaustion in CD8 T-cells [60]. HCV infections may also influence HIV disease progression. In a large cohort study the risk of HIV- and AIDS-related death was higher among HCV/HIV-coinfected individuals than among HIV-monoinfected individuals [61], regardless of risk population.

Treatment

The objective of HCV treatment is HCV RNA eradication; a sustained viral response (SVR), undetectable HCV RNA in serum 12 weeks after treatment with DAA (24 weeks in the era of interferon based therapies) [62], is considered an indicator of effective treatment [63]. Most HCV-infected persons are diagnosed in the chronic phase of infection and as such are no longer expected to clear the virus spontaneously. For these patients, treatment can stop

disease progression and reverse complications [64]. For those diagnosed in the acute phase of infection (first 6 months after infection), it is according to international guidelines advised to postpone treatment initiation and await possible spontaneous clearance of the virus [65]. Since 1998, HCV infection could be treated relatively successfully with combination therapy of interferon and ribavirin [66]. From 2001 on the pegylation of interferon (peginterferon) further improved virological response [67, 68]. The SVR rate for the treatment of chronic HCV monoinfection with peginterferon and ribavirin ranged from 46% for genotype 1 to 76% for genotypes 2 and 3 [67]. Treatment of acute HCV monoinfection with this combination therapy had comparable or higher success rates [69]. Disadvantages of peginterferon and ribavirin are the route of administration (interferon needs injecting), the presumed need of long treatment periods (6-12 months), the limited treatment response in certain genotypes [70], the serious side-effects such as depression and anemia [71], and the limited accessibility due to high cost of peginterferon [72] .
Fortunately, in recent years there has been a rapid development of DAA, new antiviral therapies that need shorter treatment periods (8-12 weeks). DAA are more successful and current DAA cause hardly any side-effects (figure 2) [29, 73]. DAA target specific nonstructural proteins of the virus, which leads to the interruption of viral replication and infection [74]. Telaprevir and boceprevir were the first generation DAA to be available and licensed for treatment of chronic HCV infection [75, 76]. Both telaprevir and boceprevir are no longer used due to side effects, and are replaced by a wide range of new DAA which have been approved for use and have been implemented. Current treatment regimens consist of a combination of two or more DAA (mostly without ribavirin), depending on genotype and presence and severity of liver fibrosis/cirrhosis [65]. Cure rates with DAA can be as high as 95% [73]. While former HCV treatment regimens for the treatment of chronic HCV were less successful in HIV-coinfected individuals compared to HCV-monoinfected individuals [77], the success rates of the current DAA regimens are comparable between these groups [78-80]. Clearance of HCV infection after either peginterferon/ribavirin or DAA treatment in both monoinfected and coinfected patients is associated with reduction and frequently regression of liver disease [81, 82]. In coinfected patients, drug-to-drug-interaction between DAA and cART needs attention, although the occurrence of interaction appears to be limited [83].

At first, the high costs of DAA treatment led to a prioritization of treatment initiation for those with the highest risk of morbidity and mortality (patient with severe fibrosis), who therefore benefit most of HCV clearance on the short term. The most recent guidelines of the American Association for the Study of Liver Diseases (AASLD) no longer recommend this prioritization and propose treatment for almost all patients with chronic HCV [65]. In the Netherlands DAA treatment was reimbursed to patients with severe liver fibrosis since 2014 and to all patients, regardless of fibrosis stage, since October 2015 [84].

In specific populations with a high risk of transmission, such as HIV-infected MSM, treatment in the acute phase may be indicated from a public health perspective [84-86]. Although DAA are not yet licensed for treatment of acute HCV infection, there will be hardly any delay in starting DAA in this particular group, since in practice a person is often diagnosed 3-6 months after infection and will start DAA 4-8 weeks later, when no spontaneous clearance is observed (i.e. the demarcation of becoming a chronic infection) (personal communication K. Brinkman).

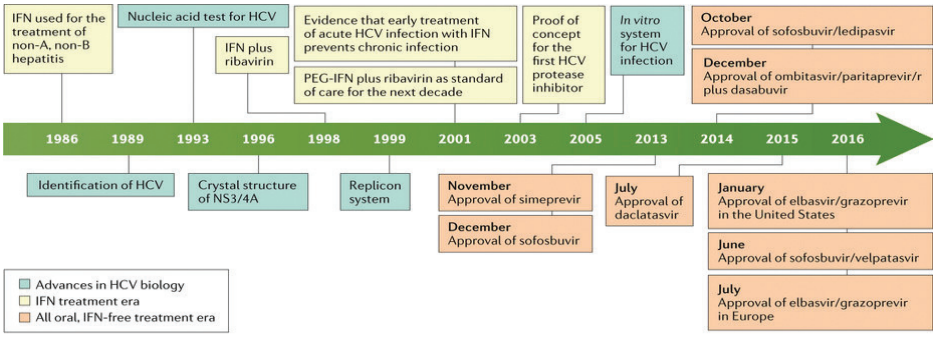

Figure 2. Milestones in HCV research and management; Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Disease Primers, copyright 2017.

Prevention

Contrary to hepatitis A and B no vaccination exists to prevent HCV infection. The genetic heterogeneity of the virus enables the creation of enough escape mutations to evade the immune response [87]. This makes the search for an effective vaccine extremely challenging [88, 89].

Primary prevention of HCV can be achieved by preventing blood-to-blood contact as described above, e.g.: availability of screened blood products, implementation of hygienic measures in health care settings, harm reduction programmes including needle and syringe exchange for PWID, the use of condoms when having male-to-male sex.

Secondary prevention is accomplished by testing and treatment of risk groups. One of the greatest barriers in controlling the global HCV epidemic is the prevailing unawareness of HCV status among infected persons, due to the asymptomatic nature of infection. Therefore, increasing efforts have been made in recent years to enhance testing of the population at risk [90-93]. Frequent diagnosis and prompt treatment of acute and chronic HCV infection lead to a decrease of onward infection risk on a population level through prevention of secondary transmission [94-96].

Reduction of the worldwide HCV epidemic remains a challenge as long as access to these prevention measures and treatment is limited because of lacking awareness, stigmatization, criminalization of key populations, and high treatment costs [97, 98].

1.2 Hepatitis C virus epidemics in the Netherlands, specifically Amsterdam

In the past two decades an expanding number of studies have been performed on HCV incidence and prevalence in the Netherlands. Before the recognition of HCV in 1989 the main groups affected in the Netherlands were persons infected through blood products (often haemophiliacs) or surgical procedures, and PWID through sharing of injecting equipment. Since the introduction of HCV screening of blood products and implementation of hygienic measures, transmission through blood products and medical procedures has become rare in the Netherlands [99]. Likewise, HCV transmission through injection drug use has decreased substantially since 1990, probably due to the increasing coverage of adequate comprehensive harm reduction and a decrease of popularity of injection drug use in general [17, 100, 101]. Hardly any new HCV infections in the PWID group were observed in recent years [102]. HIV-infected MSM have become a new risk group in Amsterdam and elsewhere in the Netherlands since the beginning of this century and are momentarily considered the group with the highest HCV incidence in the Netherlands [103, 104]. In 2017, 58 new acute HCV infections were notified, of which 67% were among MSM [105].
Recent estimates indicate that the prevalence of chronic HCV infection (HCV RNA positive persons) in the Netherlands is 0.16%, corresponding with approximately 23.000 persons. Non-western first generation immigrants account for 60% of this group [106]. Despite declined incidence, (former) PWID constitute the population with the second largest prevalence (15%). HIV-infected MSM constitute 2.9% of the total prevalence. Studies described in this thesis focus on the epidemics and consequences of HCV infection in PWID and HIV-infected MSM in Amsterdam.

HCV epidemiology among PWID

From the second half of the nineteen seventies, after the introduction of heroin, a diverse population of hard drug users expanded in Amsterdam. The number of drug users rose to approximately 10.000 in 1980, causing both a public health burden and a rise in criminal activities [107]. The local authorities decided to start the supply of methadone in the hope of establishing harm reduction with regard to the drug users' health and the public safety. The number of hard drug users decreased. However, mainly as a consequence of sharing injecting equipment and unsafe sex through prostitution this vulnerable population was hit

by the HIV epidemic [108], and, in hindsight, even earlier by the HCV epidemic. Needle and syringe exchange programmes to prevent infectious diseases such as Hepatitis B, C and HIV, were introduced in the mid-eighties [109]. In December 1985 the Amsterdam Cohort Studies (ACS) on HIV started enrolment of injecting and non-injecting drug using people [108]. At enrolment, the HIV seroprevalence among PWID was 28% and the HCV seroprevalence 74% [110]. HCV incidence dropped from 27/100 person years (PY) (late 1980s) to 2/100 PY 20 years later [100], but the HCV RNA prevalence was estimated to be still 59% among ever-injectors in 2016 [106]

HCV risk factors and prevention among PWID

Although the incidence of HCV and also HIV has declined among PWID over time [111], for the chronically infected group that continues to inject drugs, opioid substitution treatment (OST) and needle and syringe exchange programmes are still needed to prevent either HCV reinfection after successful treatment, HCV superinfection, or spread of HIV and HCV among peers [112]. In the PWID population in the Netherlands, treatment of HIV and HCV may not have played a large role in halting the epidemic [113, 114], but it attributed to prevention of disease complications such as AIDS and liver failure [115].

HCV testing and treatment among PWID

When the very high HCV prevalence among PWID in Amsterdam became apparent in the 1990s [111], there was no successful treatment readily available. Even when treatment with (peg)interferon and ribavirin was developed, uptake of this treatment among PWID remained extremely low [116]. Their drug use behaviour and often challenging circumstances (homelessness, comorbidity, being uninsured), were obstructing factors, limiting adherence and treatment success. Furthermore, the expectation that continued drug use would lead to reinfection made physicians reluctant to start treatment.

In 2004, to provide PWID access to low-threshold HCV testing and treatment, the Public Health Service of Amsterdam started the DUTCH-C (Drug Users Treatment of Chronic Hepatitis C) outpatient clinic at the location of the ACS among PWID, which is described more elaborate in the '*Study populations*' paragraph below. The results of the DUTCH-C project and related study are described in this thesis (chapter 2.2) [117].

HCV epidemiology among HIV-infected MSM

In 2005 the first report from the Netherlands was published describing sexual transmission of HCV among HIV-infected MSM in Rotterdam, the Netherlands [118]. The appearance of subsequent reports from the UK, Germany, France, Swiss, the USA and Australia [119-123] revealed the emergence of a global epidemic of HCV among HIV-infected MSM in urban settings [124]. Retrospective testing demonstrated that the increase in HCV incidence among

this population had already started in the mid-nineties [34], and possibly even eighties in the USA [125]. In a meta-analysis of 28 original studies, published between 2000 and 2016, the pooled HCV incidence among HIV-infected MSM was estimated at 0.78/100 PY, with a range from 0 (in a small Australian cohort) to 2.35/100 PY [126]. Another meta-analysis of 15 unique studies estimated an incidence rate of 1.34/100 PY in 2012 [35].
Recent studies indicate that the epidemic may be levelling off in Western Europe [127, 128]. However, as described in this thesis (chapter 3.2), and observed elsewhere, reinfection rates are high [129, 130] and, as stated earlier, the epidemic seems to be on the rise in other regions, such as in Japan, Taiwan and Thailand [36, 37, 131].

HCV risk factors among MSM

Traditional risk factors such as blood transfusion and injection drug use as a possible route of transmission were denied by most HCV-infected MSM participating in a study on HCV incidence [38]. In case-control studies among MSM HCV infection was associated with: being HIV-infected, sexual behaviour causing mucosal damage, such as group sex, fisting and toys use, ulcerative sexually transmitted diseases, and non-injecting drug use before or during sex [38, 123, 132]. Phylogenetic studies demonstrated the existence of specific international clusters of HCV-infected MSM [124], and no overlap with PWID networks [133], supporting the hypothesis that in MSM transmission takes place during sexual activities. Despite these findings, debate about the route of transmission and specific HCV risk factors in this population still continued. The fact that HCV-infected persons often practice multiple risk behaviour at the same time [26] makes it difficult to disentangle direct and indirect causes of transmission.

HCV prevention in MSM

Different methods may prevent further spread of HCV infection among MSM. Primary prevention comprises implementation of risk reduction strategies such as use of condoms and minimizing mucosal damage during sex. To motivate men to implement risk reduction, raising awareness and increasing knowledge about HCV and prevention methods are essential. In the Netherlands, written information about HCV was first published by the Public Health Service Amsterdam and HIV Association [134] and provided at STI and HIV outpatient clinics, through the internet and at gay venues.
Similar to the population of PWID, secondary prevention of HCV among MSM includes HCV testing and treatment. When testing leads to early diagnosis, implementation of risk reduction and treatment, it may play an important role in limiting the epidemic by lowering the infection risk in the community [95, 135].

HCV testing and treatment in MSM

Developing optimal testing for (HIV-infected) MSM, possibly in the form of screening programmes, may attribute to HCV prevention. The AASLD recommends all newly diagnosed HIV individuals to be screened for HCV antibodies. Furthermore, HIV-infected MSM who have unprotected sex are advised to repeat testing at least annually [65]. European guidelines for sexual health settings recommend MSM who continue HCV risk behaviour or who have been previously HCV infected to perform HCV RNA testing every three months [136].

Whether screening actually influences the further spread of the epidemic depends on several factors including the stage of the epidemic, the test frequency, the quality/type of tests, risk reduction following diagnosis, and time to treatment initiation. The dynamic nature of these factors creates an ongoing challenge regarding the optimization of screening and treatment.

The availability of DAA is of great benefit for the HIV/HCV-coinfected MSM population, of whom the majority already is in clinical care. HCV micro- elimination is therefore considered an achievable goal in this population, if efforts to increase testing and prompt treatment are continued [137-139] in combination with effective behavioural interventions [135, 140].

1.3 Aims, study populations and outline of thesis

Aims

The studies in this thesis were conducted to improve the prevention and disease management of HCV infection in two key populations in the Netherlands: PWID and MSM with HIV-infection. The HCV epidemic among PWID is well mapped with limited ongoing transmission in the Netherlands, but treatment of this population needs to be enhanced. Exploring the possibility of integrating care in existent harm reduction programmes, providing services to this group, was a first step to accomplish this. The HCV epidemic among HIV-infected MSM poses challenges from another perspective. The optimization of prevention strategies is only possible when the dynamics of this evolving epidemic are better understood. Essential steppingstones in this process are mapping the spread of primary infections and reinfections, understanding the risk factors for HCV infection and the knowledge on this topic of men at risk, and exploring the motives for and barriers to risk reduction. Furthermore, since the HCV epidemic is still ongoing among MSM, guidelines to identify MSM at risk of HCV infection and optimize testing and treatment uptake should be improved.

Study populations

The studies described in this thesis have been performed in four cohorts, outlined in table 1:

Amsterdam Cohort Study (ACS) among MSM

In 1984, three years after the first patient with AIDS had been diagnosed in the Netherlands, the Amsterdam Cohort Study on HIV among MSM was initiated by the Public Health Service Amsterdam, Academic Medical Center and Sanquin Blood Supply Foundation [141]. It is an ongoing prospective cohort study with the initial aim to study prevalence, incidence and risk factors of HIV and AIDS, the (natural) history and pathogenesis of HIV infection, and to evaluate the effects of interventions. Today, bloodborne-infections and sexually transmitted infections other than HIV are also studied. Both HIV-infected and uninfected MSM have been enrolled. Clinical, epidemiological and behavioural data are collected every 6 months, as well as blood samples for virological and immunological testing and storage.

Amsterdam Cohort Study (ACS) among people who (previously) injected drugs (PWID)

A second cohort with comparable aims among people who used drugs was initiated one year later [92]. Alike the MSM cohort it was an open and prospective observational cohort study that included both HIV-uninfected and HIV-infected individuals. In contrast to the continuing spread of HIV and HCV infections among MSM, there were very few new HIV and HCV infections found among PWID in the past decade [111]. This was the main reason to close the cohort of PWID in 2016.

Drug Users Treatment of Chronic Hepatitis C (DUTCH-C) unit

In 2004, to provide PWID access to low-threshold HCV testing and treatment, the Public Health Service of Amsterdam started the DUTCH-C outpatient clinic at the location of the ACS PWID cohort, in collaboration with the Academic Medical Center in Amsterdam. PWID were included from the ACS or were referred from methadone clinics in Amsterdam. All participants were offered HCV testing and if applicable treatment at the unit. The testing and treatment was embedded in a research protocol linked to the research already performed in the cohort. From 2014 onwards the DUTCH-C project was ended and HCV care is since then coordinated by a nurse of the Mental Health department of the Public Health Service of Amsterdam. HCV treatment itself is since then provided by hepatologists or infectious disease specialists in hospitals.

MSM Observational Study of Acute Infection with hepatitis C (MOSAIC)

The MOSAIC study was set up in 2009 to study the current epidemic and sequelae of hepatitis C co-infection among HIV-infected MSM in the Netherlands. The original aims of this study were to unravel determinants/risk factors of acute HCV infection in MSM, to study

therapy outcome of acute HCV infection in HIV-infected patients, to establish frequency and consequences of HCV re- and/or superinfection and to study the impact of HCV on morbidity and mortality in HIV-infected MSM.
It was an open, prospective, comparative observational cohort study. Initially we included HIV-infected MSM with HCV coinfection and, as controls, HIV-infected MSM that were not HCV infected. The MOSAIC was a collaboration between the Public Health Service of Amsterdam, several large HIV outpatient clinics in the Netherlands (Academic Medical Center, OLVG, Slotervaart hospital and DC-clinic in Amsterdam, Erasmus Medical Center in Rotterdam and University Medical Center in Utrecht), and the Dutch HIV Monitoring Foundation. The data collection took place during regular visits at the HIV outpatient clinics and included HCV-related testing, collection of blood samples, administration of questionnaires on risk behaviour, quality of life and depression, and clinical outcomes (HCV and/or HIV treatment, side-effects, comorbidity, fibrosis).

Outline per chapter

The prevalence of HIV and HCV infection among (ever-)PWID is high compared to other key populations. Still, PWID are not as likely to be treated as others [97, 142]. Expectations among physicians about PWIDs´ treatment willingness, adherence and success have been low [143], especially if someone still injected drugs. In **chapter 2** factors were studied that are associated with adherence to HIV therapy and success of HCV therapy in (former) drug users in Amsterdam, with the goal to further improve treatment programmes in this vulnerable population. In the study presented in **chapter 2.1** we evaluated the influence of different levels of harm reduction on cART-adherence among HIV-infected PWID. **Chapter 2.2** describes the development, implementation and results of the multidisciplinary HCV treatment programme for HCV-infected PWID (DUTCH-C) in Amsterdam.

The recent epidemic of HCV among HIV-infected MSM has led to a wide range of research questions. In **chapter 3** studies are presented that investigated the incidence and treatment of HCV infection in this population in the Netherlands. In **Chapter 3.1** we focused on incidence of primary HCV infection, as a follow-up of the initial study by van de Laar et al. [38], that showed the initial rise in HCV incidence in Amsterdam. In **Chapter 3.2** we examined the rates of HCV reinfection after successful treatment in this population. In **chapter 3.3** the effect of HCV treatment duration was investigated among MSM with acute HCV infection and treated with peginterferon and ribavirin.

In order to develop effective prevention strategies, we should understand more about the risk factors associated with HCV infection (and reinfection) among MSM and the awareness and knowledge MSM have on this topic. **Chapter 4** looked into all these connected themes

in this population. **Chapter 4.1** examined which factors are associated with acute HCV infection. In **chapter 4.2** the degrees of awareness of and knowledge of HCV infection were studied among predominantly HIV- and HCV-uninfected MSM. In **chapter 4.3** the impact of HCV infection on sexual risk behaviour of HIV-coinfected MSM was explored using qualitative methods.

In **chapter 5**, the general discussion, the outcomes of the presented studies are discussed in relation to recent literature and healthcare developments. The implications for public health (specifically prevention, including testing, and treatment) and recommendations for healthcare policy and future research are specified.

Table 1. Data sources used in this thesis

Chapter	Study name	Study population and site	Design	Study period
2.1	ACS PWID	HIV-infected (ever) injecting drug users, Public Health Service of Amsterdam, the Netherlands	Observational cohort study	1999-2009
2.2	DUTCH-C	Drug users tested and treated for HCV at the Public Health Service of Amsterdam, the Netherlands	Demonstration study offering HCV testing and treatment	2004-2011
3.1	ACS MSM	HIV-uninfected and HIV-infected MSM, Public Health Service of Amsterdam, the Netherlands	Observational cohort study	1984-2012
3.2	MOSAIC	HIV-infected MSM treated for HCV infection in five HIV outpatient clinics, the Netherlands	Longitudinal study	2003-2011
3.3	MOSAIC	HIV-infected MSM treated for HCV infection in two HIV outpatient clinics, the Netherlands	Longitudinal study	2003-2009
4.1	MOSAIC	HIV-infected MSM with HCV infection and HIV-infected MSM without HCV infection in five HIV outpatient clinics, the Netherlands	Cross sectional study	2009-2014
4.2	ACS MSM	HIV-uninfected and HIV-infected MSM, Public Health Service of Amsterdam, the Netherlands	Cross sectional study	2007-2010
4.3	MOSAIC/HIV outpatient clinics/ HIV Association	HIV-infected and HIV-uninfected MSM with (previous) HCV infection, the Netherlands	Qualitative study	2011-2012

ACS: Amsterdam Cohort Studies
DUTCH-C: Drug Users Treatment of Chronic Hepatitis C
HCV: hepatitis C virus
HIV: human immunodeficiency virus
MOSAIC: MSM Observational Study of Acute Infection with hepatitis C
MSM: men who have sex with men
PWID: people who (previously) inject(ed) drugs

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Chapter 2

Optimizing care for HIV- and HCV-infected people who use drugs

Chapter 2.1

Harm reduction intensity– Its role in HAART adherence amongst drug users in Amsterdam

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Abstract

Background

Opioid substitution treatment seems to improve adherence to highly active antiretroviral therapy (HAART) in drug users (DU). DU in Amsterdam receive methadone within a harm reduction programme. We hypothesized that not only receiving methadone, but joining this complete comprehensive programme would improve HAART adherence.

Methods

Included were 102 HIV-positive DU attending the Amsterdam Cohort Study (ACS), reporting HAART use at multiple visits between 1999 and 2009. Non-adherence was defined as taking less than 95% of medication in the past 6 months (self-reported). Harm reduction intensity (HR) was measured by combining injecting drug use, methadone dosage and needle exchange, in different levels of participation, ranging from no/incomplete HR, complete HR to low or no dependence on HR. We studied the association between non-adherence and harm reduction intensities with logistic regression models adjusted for repeated measurements.

Results

Non-adherence was reported in 11.9% of ACS visits. Non-injecting DU with low dependence on HR were less adherent than DU with complete HR (aOR 1.78; CI 95% 1.00–3.16), although there was no overall effect of HR. No difference was demonstrated in adherence between DU with complete HR and incomplete HR. Unsupervised housing (no access to structural support at home) (aOR 2.58; CI 95% 1.40–4.73) and having a steady partner (aOR 0.48; CI 95% 0.24–0.96) were significantly associated with respectively more and less non-adherence.

Conclusions

In Amsterdam, still-injecting DU who are exposed to systematic and integrated care, although not practising complete harm reduction, can be just as adherent to HAART as DU who make use of complete harm reduction and non-injecting DU with no dependence on harm reduction. These findings suggest the importance of a systematic and comprehensive support system including supervised housing and social and medical support to increase HAART adherence rates amongst all HIV-infected DU. When such programmes are introduced in settings where injecting drug use is highly prevalent, access to HAART for drug users in these settings can and should be increased.

Introduction

Since the introduction of highly active antiretroviral therapy (HAART), studies concerning the social and behavioural aspects of HIV have extended their interest to aspects that have impact on HIV treatment, such as HAART adherence. High adherence rates are necessary to attain sustained HIV viral load suppression and prevent drug resistance [1-3].

The negative perception of physicians about HAART adherence amongst drug users is one of the reasons drug users still have less and later access to HAART compared to non-drug using HIV-patients [4-6]. Although the clinical benefits of HAART treatment in drug users related to HIV-specific death have shown to be present as in other HIV-patients [7], drug users eventually benefit less from HAART on the population level, partly because of the barrier to HAART access.

Several studies indeed demonstrate an association between drug use and non-adherence [8-13]. The treatment of illicit drug use with opioid substitution has therefore been proposed as a strategy that may not only lower the HIV incidence in combination with other harm reduction components [14], but may also be a determinant that positively influences adherence to HAART, and it has proven to be so in several studies [15-20]. Its effect varies though as to the structure of care [18] and whether the patient is a former or a current user of illicit drugs [16].

In the Amsterdam Cohort Study (ACS) amongst drug users, we follow drug users who have access to HIV care and drug addiction care outside the cohort setting. Drug addiction care consists of opioid substitution treatment with methadone, needle exchange programmes (NEP), and medical and social care. The intensity of contact with the health care system and the kind of health care a drug user receives depends on the level of drug dependence and personal 'stability' of the drug user, defined by, e.g. (psychiatric) comorbidity, social network and housing situation and the level of financial independence. The result is a low-threshold individualized treatment approach with different intensities of harm reduction in which active drug use is not considered an exclusion criterion for treatment.

We previously demonstrated that full participation in such a harm reduction programme, and not the use of needle exchange programmes or methadone alone, is associated with a lower HIV and HCV incidence, indicating that combined prevention measures are effective [14]. Here, we hypothesized that full participation in such a comprehensive harm reduction programme including medical and social care would improve adherence to HAART. The current study therefore aimed to investigate determinants that influence adherence to HAART in HIV-positive drug users in Amsterdam, and specifically their usage of different intensities of harm reduction.

Methods

Study population and design

The ACS amongst drug users is an open, prospective cohort study. It was initiated in 1985 to study the epidemiology of HIV and other bloodborne and sexually transmitted infectious diseases and to evaluate the effects of interventions, such as prevention and treatment. The recruitment of participants is still ongoing [21]. Participation in the cohort is voluntary, and informed consent is obtained. During the study period of 1999–2009, inclusion criteria consisted of: having a history of regular illicit drug use, either injecting or non-injecting, living in the Netherlands, being motivated to participate in the study every 6 months and accepting to receive HIV-test results. Participants receive a financial compensation at every follow-up visit. At study entry and follow-up visits every 6 months, the participant answers standardized questions asked by a trained nurse. Questions concern demographics, drug behaviour, sexual behaviour, and medical history, including HIV- and drug-addiction treatment, medication and adherence, all referring to the time-period between the current and previous visit (past six months).

Each visit a blood sample is drawn for HIV testing and storage. For HIV-positive participants, viral load is tested, using Nuclisens HIV1 QT until 2006 and, thereafter, M2000rt (Abbott). The CD4 count is determined using flow cytometry.

The present study included participants who were HIV-positive and were prescribed HAART during the period of January 1999 (start collection of adherence-data) until February 2009. Whether a participant used HAART or not was based on self-report and confirmed by checking clinical data from medical records received after hospital admission and yearly matching against the national HIV register.

Definition of variables

Rates of non-adherence to HAART were self-reported by the participant to the study nurse and are based on the number of days that medication was not taken in the last 6 months. The reported number was subsequently recorded as one of four categories. To calculate the percentage of non-adherence in the last 6 months the number of days in the category was divided by 6 months. For our analyses a participant was considered non-adherent if taking less than 95% of the prescribed medication [2].

To study the impact of different intensities of harm reduction on adherence, we combined three main determinants of harm reduction intensity in our cohort: injecting of drugs (IDU) or not, use of a needle exchange programme (in which irregular needle exchange means less than 100% of needles exchanged) and methadone-dosage. We assumed 80 mg/day as the minimum sufficient dosage to achieve harm reduction [9, 22, 23].

With these determinants we defined four categories of harm reduction intensity, comparable to those previously associated with HIV and HCV incidence [24]: 'No/incomplete harm reduction' defined as injecting drugs in past 6 months, no needle exchange and no methadone/injecting drugs in past 6 months, any methadone dose and no or irregular needle exchange; or injecting drugs in past 6 months and low methadone dose and always needle exchange, 'complete harm reduction' defined as injecting drugs, high methadone dosage (80 mg/day) and full needle exchange; or not injecting drugs and high methadone dosage, 'low dependence on harm reduction' defined as not injecting drugs, low methadone dosage (<80 mg/day), and 'no dependence on harm reduction' defined as not injecting drugs, no methadone.

Statistical analysis

Chi-square test and Mann–Whitney's U-test were used to compare characteristics of HIV-positive DU receiving HAART on their first HAART ACS visit after 1998 and characteristics of those never receiving HAART on their first ACS visit after 1998. CD4 count and viral load were compared between the first HAART visit of HAART-users and the last visit of non-HAART users. General characteristics that were evaluated besides harm reduction intensity in the past 6 months included sex, age at visit, ethnicity, having a steady partner in the past 6 months, housing situation in the past 6 months, drug use (frequency, type of drugs, mode of use) in the past 6 months, methadone use in the past 6 months, needle exchange use in the past 6 months, viral load as measured at visit, CD4 count as measured at visit.

The Kaplan–Meier method was used to estimate the cumulative incidence of non-adherence. Follow-up time was calculated from the date of the first visit on HAART until the earliest of: non- adherence, loss to follow-up, or the censoring date (February 2009). To test differences in percentages of viral load and CD4 count between adherent persons and non-adherent persons, stratified by harm reduction intensity, we used univariate logistic regression. Finally, univariate and multivariate logistic regression was used to study the association between harm reduction intensity and non-adherence (the reference category being complete harm reduction, because of group size), and other potential determinants and non-adherence. Generalized Estimating Equations (GEE) [25], using the exchangeable working correlation matrix, were applied to all logistic regression analyses to correct for repeated measurements within individuals.

Since we were primarily interested in the independent role of harm reduction intensity, this variable was always included in our first multivariate model. We also always included calendar year, since intake of HAART medication became less complex over time, which might have influenced adherence. We extended this model with considering all other variables with a p-value 0.10 in univariate analysis and/or variables assumed to be related to non-adherence (based on the literature: having a steady partner [26, 27], housing situation

[28], and gender [8, 29]) for entry in our final model. This multivariate model was built using a stepwise backward strategy. In our final model, we checked for interaction between variables and for confounding. A p-value 0.05 was considered statistically significant.
Besides harm reduction intensity, we studied the effects of the underlying individual components of the harm reduction programme (IDU, methadone dosage, NEP) and non-injecting drug use. Therefore we conducted a second multivariate analysis to evaluate the separate effect of these variables. All analyses were conducted using SPSS 15, STATA 9.2 and R 2.7.

Results

Characteristics

Between January 1999 and February 2009, 934 drug users were followed in the ACS, of whom 157 were HIV-positive. In this period, 102 of the HIV-positive drug users reported using HAART of whom 101 answered questions about adherence to HAART.
The CD4 counts of HIV-positive drug users that did not use HAART (n = 55), as measured on their last visit in the studied period (median 250 cells/µl, IQR 280), were comparable to the CD4 counts of those using HAART, as measured on their first HAART-visit (median 250 cells/µl, IQR 233). However, the drug users never receiving HAART had significantly higher viral load levels (median 24,000 copies/mL IQR 113250 vs. median 400 copies/mL IQR 950). Participants never receiving HAART also were significantly more likely to have injected drugs and to have joined an incomplete harm reduction programme in the past 6 months. In addition, they received methadone less often (borderline significance) compared to those participants on HAART (data not shown).
Of the 102 HIV-positive drug users using HAART, the total number of visits since 1998 was 1376, of which 733 were HAART-visits. The median number of HAART-visits since 1998 was 5 (IQR 6), and median time of follow-up since the first HAART-visit was 3 years (IQR 4.6) (see Table 1). The median time between HAART-visits was 181 days (IQR 102).
Included were 71 men and 31 women, and mean age was 42.3 years (SD 6.4 years). The majority (92.2%) reported having ever injected illicit drugs (defined by usage of heroin, cocaine or speed-ball, a mix of both). Of all participants, 31.4% reported having injected illicit drugs in the 6 months preceding their first HAART-visit, and 65.7% reported having used illicit drugs in a non-injecting manner. The majority (89.2%) used methadone in some dosage. According to our harm reduction intensity definitions, 14.7% of participants were included in the no/incomplete harm reduction category at their first HAART visit; 52.9% were included in the complete harm reduction category; 24.5% had a low dependence on harm reduction, and only 7% had no dependence on harm reduction at the first HAART visit.

Non-adherence, viral load and CD4 count

According to our definition, non-adherence in the past 6 months occurred during 11.9% of all visits. During the total studied period, the rate of non-adherence ranged from a minimum rate of 6.2% (in 2002) to a maximum rate of 18.9% (in 2005) of the visits per year. Of the 76 participants who were adherent on their first included visit and who had a follow-up visit, 26 became non-adherent at least once in the study period. Fig. 1 shows that at 3 years the cumulative incidence of non-adherence was 32% (95% CI 20–43%) and at 7 years it was 44% (95% CI 30–58%).

Table 2 shows that non-adherence was significantly associated with higher viral load level (p = 0.008). This applies to both the active injecting drug users in the no/incomplete HR intensity as former injecting drug users in the low dependence on HR intensity. There was no significant association between non-adherence and CD4 count.

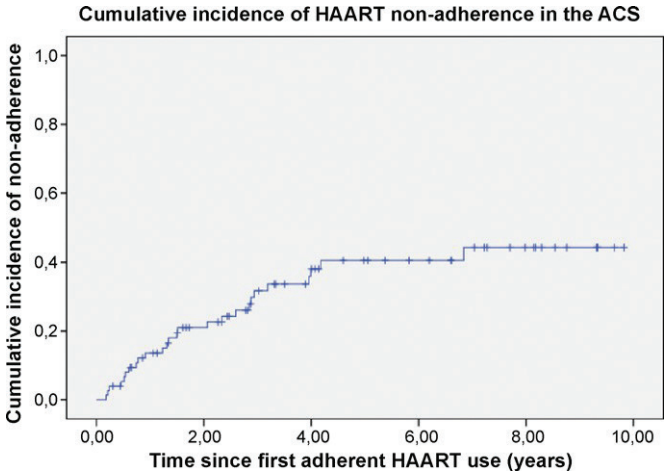

Figure 1. Cumulative incidence of non-adherence to HAART amongst drug users in the ACS from January 1999 until February 2009.

Harm reduction intensity and determinants of non-adherence

Both univariate and multivariate analyses (Table 3) showed no overall significant effect of harm reduction intensity on non-adherence (p = 0.07 and 0.17 respectively). Interestingly, in univariate analysis, drug users with low dependence on harm reduction (i.e., non-injectors with low methadone dosing) seemed to be more likely to be non-adherent to HAART, compared to drug users with complete harm reduction (OR 2.03; 95% CI 1.12–3.69). This trend remained in multivariate analysis (adjusted (a) OR 1.78; 95% CI 1.00–3.16).

Furthermore, drug users living in a situation without access to structural support at home (unsupervised housing) were significantly more likely to be non-adherent (aOR 2.58: 95%

CI 1.40–4.73). Participants having a steady partner in the last 6 months before an ACS visit appeared to be less non-adherent than the participants having no steady partner (aOR 0.48; 95% CI 0.24–0.96). Female participants tended to be more non-adherent than male participants, although the effect was borderline significant (aOR 1.98: 95% CI 0.95–4.14).
Multivariate analysis determining the influence of each individual component of harm reduction on non-adherence revealed no significant associations between any drug use (heroin, cocaine, benzodiazepines or stimulants) and non-adherence. Participants taking higher doses of methadone were significantly more adherent in univariate analysis (p = 0.02) compared to participants taking a lower dose of methadone (see Table 4), but this effect became non-significant in multivariate analysis. The effect of sex, steady partner, housing situation and time period was comparable to the model including harm reduction intensity, although the effect of sex reached statistical significance in the second multivariate model. Finally, since there was just a small number of visits in which participants reported to have received no harm reduction at all, we repeated our analysis without these visits in the harm reduction variable. The results were not different from analysis with the total group.
In sensitivity analysis, results also appeared to be comparable when other criteria defined non-adherence (less than 100% of medication or less than 92% of medication taken).

Table 1. Characteristics of HIV-positive drug users of the Amsterdam Cohort Studies using HAART between January 1999 and February 2009.

	First visit ***N*** **(%)** **(number of persons = 102)**	**All visits** ***N*** **(%)** **(number of visits = 733)**
Sex		
Female	31 (30.4)	227 (31.0)
Age at visit		
Mean in years (SD)	42.3 (6.4)	44.1 (5.7)
≥29 and <40	42 (41.2)	178 (24.3)
≥40 and <50	48 (41.7)	445 (60.7)
≥50	12 (11.8)	110 (15.0)
Nationality		
Non-Dutch	16 (15.7)	86 (11.7)
Education[a]		
Median in years (IQR)	4.0 (3.0)	4.0 (3.0)
≤1 year	10 (9.8)	70 (9.6)
1–7 years	78 (76.5)	550 (75.0)
≥7 years	14 (13.7)	113 (15.4)

Table 1. Continued.

	First visit ***N*** **(%)** **(number of persons = 102)**	**All visits** ***N*** **(%)** **(number of visits = 733)**
Housing in past 6 months		
Unsupervised housing[b]	76 (74.5)	499 (68.4)
Steady partner in past 6 months		
Yes	41 (40.2)	242 (33.0)
Harm reduction intensity in past 6 months		
No/incomplete	15 (14.7)[f]	81 (11.1)[g]
Complete	54 (52.9)	452 (61.7)
Low dependence	25 (24.5)	153 (20.9)
No dependence	7 (6.9)	41 (5.6)
Methadone usage in past 6 months		
Yes	91 (89.2)	683 (93.2)
Methadone dosage in past 6 months		
Median (IQR)	100 mg/d (65 mg/d)	100 mg/d (80 mg/d)
1–70 mg/d	28 (27.5)	198 (27.0)
71–100 mg/d	34 (33.3)	184 (25.1)
101–150 mg/d	17 (16.7)	140 (19.1)
151–315 mg/d	12 (11.8)	161 (22.0)
Needle exchange (NE) in past 6 months		
No IDU, no NE	70 (68.6)	551 (75.2)
IDU, no NE	7 (6.9)	26 (3.5)
IDU, irregular NE	3 (2.9)	10 (1.4)
IDU, full NE	22 (21.6)	143 (19.5)
Any drug use in past 6 months[c]		
Yes	76 (74.5)	574 (78.3)
Ever injected		
Yes	94 (92.2)	675 (92.1)
Injected in past 6 months		
Yes	32 (31.4)	178 (24.3)
Drug injected in past 6 months		
Heroin		
Yes	7 (6.9)	42 (5.7)

Table 1. Continued.

	First visit ***N*** **(%)** **(number of persons = 102)**	**All visits** ***N*** **(%)** **(number of visits = 733)**
Cocaine		
Yes	14 (13.7)	89 (12.1)
Heroin + Cocaine (speedball)		
Yes	18 (17.6)	99 (13.5)
Amphetamines		
Yes	3 (3.0)	16 (2.2)
Non-injecting drug use in past 6 months		
Heroin		
Yes	40 (39.2)	260 (35.5)
Cocaine		
Yes	60 (58.8)	
Heroin + cocaine (speedball)		
Yes	2 (1.9)	10 (1.4)
Amphetamines		
Yes	0 (0.0)	8 (1.1)
Barbiturates		
Yes	10 (9.9)	134 (18.7)
Tranquilizers (benzodiazepines)		
Yes[d]	60 (59.4)	421 (57.4)
Viral load at visit		
Median in copies/µl (IQR)	400 (950)	400 (578)
CD4 count at visit		
Median in cells/µl (IQR)	250 (245)	260 (231)
Number of HAART visits in 1999–2009		
Total	NA	733
Median (IQR)	NA	5 (6)
Time of follow-up since first HAART visit from 1999		
Median in years (IQR)	NA	3 (4.6)
Calendar-year of visit		
Median (IQR)	2000 (1999–2002)	2002 (2000–2006)

Table 1. Continued.

	First visit ***N*** **(%)** **(number of persons = 102)**	**All visits** ***N*** **(%)** **(number of visits = 733)**
Non-adherence to HAART in past 6 months[e]		
Yes	14 (13.7)	87 (11.9)

SD, standard deviation; IQR, inter quartile range.
a. Number of years daily schooling after 12th year.
b. Unsupervised: not living in single-bed occupancy shelter with structural support (e.g., renting own house). During this period, 7 participants reported being homeless at 1 visit, and 1 participant at 2 visits (total 1.4%). Because of this very low rate of homelessness, we included this category of housing situation within 'unsupervised' housing.
c. Injecting heroin, cocaine, methadone, and heroin and cocaine together, and non-injecting use of heroine, cocaine and heroin and cocaine together.
d. Reported use of benzodiazepines refers in most cases to benzodiazepines described by physician and not illegal use.
e. Non-adherence: taking less than 95% of prescribed HAART in the last 6 months.
f. Of 15 visits (first) in the No/Incomplete category, 3 were in the No and 12 in the Incomplete group.
g. Of 81 visits (all) in the No/Incomplete category, 6 were in the No and 75 were in the Incomplete group.

Table 2. Viral load and CD4 count stratified per harm reduction intensity and adherence.

	Total group	Non-adherent	Adherent	*p*-Value
HIV viral load	**Percentage of visits with viral load >400 × 10^8 c/µl**	**Percentage of visits with viral load >400 × 10^8 c/µl**	**Percentage of visits with viral load >400 × 10^8 c/µl**	
Overall	30% (177/594)	45% (33/73)	28% (142/515)	0.008*
Harm reduction intensity				
No/incomplete	20% (14/69)	60% (3/5)	17% (11/63)	0.036
Complete	34% (125/365)	45% (19/42)	33% (104/320)	0.006
Low dependence	22% (27/125)	41% (9/22)	18% (18/101)	0.863
No dependence	30% (10/33)	50% (2/4)	28% (8/29)	0.196
CD4 count	**Median (IQR) CD4 count × 10^6 cells/µl**	**Median (IQR) CD4 count × 10^6 cells/µl**	**Median (IQR) CD4 count × 10^6 cells/µl**	
Overall	270 (250)	255 (320)	280 (240)	0.395*
Harm reduction intensity				
No-incomplete	350 (290)	400 (337)	350 (293)	0.260
Complete	270 (220)	270 (360)	207 (220)	0.656
Low dependence	225 (233)	180 (250)	250 (238)	0.042
No dependence	430 (300)	350 (290)	430 (327)	-

IQR, inter quartile range

* *p*-Values were calculated using univariate logistic regression in a GEE model, comparing the percentages of viral load below and above 400 c/µl and comparing CD4 count above and below 200 cells/µl, between non-adherent and adherent visits.

Table 3. Prevalence of HAART non-adherence, and uni- and multivariate analyses of determinants of non-adherence amongst drug users of the ACS between January 1999 and February 2009, with harm reduction intensity and calendar year as fixed variables.

	Prevalence non-adherence (%) (*n*/visits)	OR (95% CI)	Overall *p*-value	aOR (95% CI)	Overall *p*-value
Sex			0.066		0.068
Male	9.8 (49/501)	1		1	
Female	16.9 (38/225)	1.84 (0.96–3.52)		1.98 (0.95–4.14)	
Age at visit			0.90		
≥29 and <40 years	10.1 (18/178)	1			
≥40 and < 50 years	12.5 (55/439)	1.15 (0.59–2.25)			
≥50 years	12.8 (14/109)	1.18 (0.53–2.60)			
Nationality			0.26		
Dutch	11.2 (72/641)	1			
Non-Dutch	17.7 (15/85)	1.76 (0.66–4.72)			
Education*			0.53		
≤1 year	18.6 (13/70)	1			
1–7 years	12.5 (68/544)	0.81 (0.27–2.45)			
≥7 years	5.4 (6/112)	0.46 (0.10–2.02)			
Housing in past 6 months			0.003		0.002
Supervised	7.0 (16/229)	1		1	
Unsupervised housing**	14.2 (70/494)	2.44 (1.36–4.36)		2.58 (1.40–4.73)	
Steady partner in past 6 months			0.41		0.039
No	12.4 (60/483)	1			
Yes	11.3 (27/240)	0.79 (0.44–1.40)		0.48 (0.24–0.96)	

Table 3. Continued.

	Prevalence non-adherence (%) (*n*/visits)	OR (95% CI)	Overall *p*-value	aOR (95% CI)	Overall *p*-value
Harm reduction intensity in past 6 months			0.071		0.17
No/incomplete	11.4 (6/80)	0.87 (0.35–2.18)		0.76 (0.29–2.04)	
Complete	7.5 (51/449)	1		1	
Low dependence	16.0 (24/150)	2.03 (1.12–3.69)		1.78 (1.00–3.16)	
No dependence	12.2 (5/41)	1.67 (0.66–4.24)		1.55 (0.51–4.72)	
Methadone usage in past 6 months			0.90		
No	10.9 (5/46)	1			
Yes	12.1 (82/677)	1.07 (0.38–3.06)			
Methadone dosage in past 6 months			0.021		
1–70 mg/d	14.9 (29/195)	1			
71–100 mg/d	9.8 (18/183)	0.43 (0.20–0.91)			
101–150 mg/d	11.5 (16/139)	0.47 (0.22–1.01)			
150–315 mg/d	11.9 (19/160)	0.36 (0.10–1.25)			
Needle exchange (NE) in past 6 months			0.35		
No IDU, no NE	13.0 (71/545)	1			
IDU, no NE	7.7 (2/26)	0.50 (0.13–1.96)			
IDU, irregular NE	22.2 (2/9)	1.17 (0.20–6.90)			
IDU, full NE	7.7 (11/143)	0.42 (0.16–1.13)			
Any drug use*** in past 6 months			0.90		
No	13.0 (20/154)	1			
Yes	11.6 (66/568)	1.05 (0.50–2.20)			

Table 3. Continued.

	Prevalence non-adherence (%) (*n*/visits)	OR (95% CI)	Overall *p*-value	aOR (95% CI)	Overall *p*-value
Ever injected			0.77		
No	12.5 (7/56)	1			
Yes	12.0 (80/688)	1.17 (0.48–2.91)			
Injected in past 6 months			0.13		
No	13.0 (71/546)	1			
Yes	8.5 (15/177)	0.49 (0.19–1.24)			
Drug injected in past 6 months					
Heroin			0.14		
No	11.1 (74/669)	1			
Yes	23.8 (10/42)	2.07 (0.79–5.45)			
Cocaine			0.024		
No	12.8 (80/623)	1			
Yes	4.5 (4/89)	0.21 (0.05–0.81)			
Heroin + cocaine (speedball)			0.30		
No	12.3 (76/614)	1			
Yes	9.2 (9/98)	0.63 (0.26–1.51)			
Amphetamines					
No	12.1 (84/696)				
Yes	0 (9/98)	-		-	

Table 3. Continued.

	Prevalence non-adherence (%) (*n*/visits)	OR (95% CI)	Overall *p*-value	aOR (95% CI)	Overall *p*-value
Non-injecting drug use in past 6 months					
Heroin			0.20		
No	10.6 (48/452)				
Yes	13.9 (36/259)	1.41 (0.83–2.39)			
Cocaine			0.31		
No	11.1 (28/253)	1			
Yes	12.5 (58/464)	1.34 (0.76–2.36)			
Heroin + cocaine (speedball)			0.72		
No	11.8 (83/701)	1			
Yes	10.0 (1/10)	0.67 (0.07–6.350			
Amphetamines			0.95		
No	11.8 (83/705)	1			
Yes	12.5 (1/8)	0.95 (0.20–4.55)			
Barbiturates			0.45		
No	11.9 (69/578)	1			
Yes	11.3 (15/133)	0.75 (0.36-1.57)			
Tranquilizers**** (benzodiazepines)			0.95		
No	11.2 (34/303)	1			
Yes	12.5 (52/415)	0.98 (0.59-1.65)			

Table 3. Continued.

	Prevalence non-adherence (%) (*n*/visits)	OR (95% CI)	Overall *p*-value	aOR (95% CI)	Overall *p*-value
Viral load at visit			0.014		
<400 copies/µl	9.7 (40/413)	1			
≥400 copies/µl	18.9 (33/175)	2.35 (1.28–4.29)			
Missing	10.1 (14/138)	0.93 (0.46–1.86)			
CD4 count at visit			0.30		
<200	14.8 (31/210)	1			
≥200	11.1 (44/397)	0.70 (0.40–1.21)			
Missing	10.1 (12/119)	0.54 (0.23-1.27)			
Calendar-year of visit		0.99 (0.90-1.08)	0.81	1.00 (0.91–1.10)	1.00

*Number of years daily scholing after 12th year;
**Unsupervised: not living in single-bed occupancy shelter with structural support (e.g., renting own house). During this period, 7 participants reported being homeless at 1 visit, and 1 participant at 2 visits (total 1.4%). Because of this very low rate of homelessness, we included this category of housing situation within 'unsupervised' housing;
***Injecting heroin, cocaine, methadone, and heroin and cocaine together, and non-injecting use of heroine, cocaine and heroin and cocaine together.
****Reported use of benzodiazepines refers in most cases to benzodiazepines described by physician and not illegal use.

Table 4. Prevalence of HAART non-adherence, and uni- and multivariate analyses of determinants of non-adherence amongst drug users of the ACS between January 1999 and February 2009, with methadone dosage and calendar year as fixed variables.

	Prevalence non-adherence (%) (*n*/visits)	OR (95% CI)	Overall *p*-value	aOR (95% CI)	Overall *p*-value
Methadone dosage in past months			0.021		0.13
1–70 mg	14.9 (29/195)	1		1	
71–100 mg	9.9 (18/183)	0.43 (0.20–0.92)		0.51 (0.25–1.06)	
101–150 mg	11.5 (16/139)	0.47 (0.22–1.01)		0.61 (0.27–1.34)	
151–315 mg	11.9 (19/160)	0.36 (0.10–1.25)		0.45 (0.14–1.47)	
Sex			0.066		0.038
Male	9.8 (49/501)	1		1	
Female	16.9 (38/225)	1.84 (0.96–3.52)		2.24 (1.05–4.82)	
Steady partner in past 6 months			0.41		0.039
No	12.4 (60/483)	1		1	
Yes	11.3 (27/240)	0.79 (0.44–1.40)		0.46 (0.22–0.96)	
Housing in past 6 months			0.003		0.001
Supervised	7.0 (16/229)	1		1	
Unsupervised	14.2 (70/494)	2.4 (1.36–4.36)		2.74 (1.48–5.07)	
Calendar year		0.99 (0.90–1.08)	0.81	1.00 (0.91–1.09)	1.00

Discussion

In our longstanding cohort of drug users in Amsterdam, almost all HIV-positive participants that receive HAART also rely on methadone maintenance therapy. HIV-positive drug users not receiving HAART are also less often receiving methadone treatment, even though they showed more drug use. This confirms previous findings that the use of methadone lowers the barriers to gain access to HAART [15, 17, 20].

We hypothesized that HIV-positive drug users who access a complete harm reduction programme are more adherent to HAART than those that do not. Interestingly though, we found that still-injecting drug users receiving incomplete harm reduction can be just as adherent. This might in part imply that participants of this cohort are in general more socially stable and compliant. It might also suggest that injecting drug use is not a barrier for compliance in this cohort and it should therefore not be a barrier for HIV-treatment. Furthermore, we found a tendency towards more non-adherence amongst the drug users that are presumed to have a lower dependence on harm reduction (i.e., non-injectors with lower methadone dosing) than amongst drug users with complete harm reduction including high methadone dosing. This finding has been demonstrated previously [30] and could reflect a difference in kind of health care and frequency of health care visits between those with (in)complete harm reduction and those with less dependence on harm reduction. More importantly, it might be explained by a direct effect of methadone dosing. Our model of the underlying individual components of the harm reduction programme might suggest that methadone dosage could be of a certain relevance to adherence although the effect of methadone dosage did not remain statistically significant in multivariate analysis. In our cohort, participants in the group less dependent on harm reduction, with lower methadone dosing, more often receive their methadone treatment from their general practitioner. Possibly, some general practitioners are not prescribing their patients on HAART a high enough methadone dosage, despite reports that drug users on certain combinations of HAART need an increased dosage of methadone due to its pharmaco-dynamic interaction with HAART [22, 23]. It also implies that close monitoring of patients that use both HAART and methadone is essential to prevent the detrimental consequences of a too-low methadone dosage [31]. Furthermore, using interventions such as directly administered antiretroviral therapy could attribute to the increase of adherence amongst all kind of drug users [32].
In addition, we studied variables other than harm reduction as possible determinants of HAART adherence. Firstly, the importance of a systematic support system was emphasized by the independent association of unsupervised housing with non-adherence and not having a steady partner with non-adherence. A review by Leaver et al. emphasized the 'impact of affordable and sustainable housing on the health of persons living with HIV'

[28]. With our results, we add the importance of having more health care monitoring close to home. The increased adherence of participants who live in a setting where they have access to support, such as a single-room-occupancy-shelter, probably reflects in part the direct observation of treatment, that is implemented in such housing in Amsterdam. Having a steady partner presumably leads to better adherence through social support [26, 27], and a steady partner can help by reminding to take medication and by encouragement. Overall, social and structural factors that improve or decrease adherence should gain more attention [33].

Secondly, in adjusted analyses we found no statistically significant proof of the direct influence of heroin, cocaine or other drug use on HAART adherence, even though we looked at the manner of use and sort of drug used singly and in combinations (data not shown). Obviously, in our cohort of drug users, the prevalence of injecting drugs compared to smoking or sniffing drugs is relatively low and might therefore have a less noticeable effect on adherence. In the same way, the high prevalence of non-injecting drug use might make it difficult to reveal its effect on HAART adherence in this population.

This study gains its strength from data collection over a period of ten years and the detailed data on harm reduction that allowed study of its specific influence on adherence.

A limitation is the limited sample size and more specific the near absence of a separate group of injecting drug users who receive no harm reduction and are on HAART. Using such a group as a reference would make it possible to study the influence of harm reduction in general. However, denying drug users harm reduction for study purposes in a setting where harm reduction is available would be unethical. We were nevertheless able to differentiate between intensities of harm reduction to test our hypothesis. Interestingly, the relatively small no harm reduction group appears less likely to initiate HAART in Amsterdam [20], suggesting that, besides receiving methadone, certain drug users' characteristics might influence access to harm reduction programmes and HIV care.

Another limitation is that the data on adherence are based on self-report, and over- or underreporting thus cannot be excluded. However, the fact that non-adherent participants had a significant higher viral load than participants in the adherent group indicates that the reported data are generally reliable. Also, participants were not interviewed by their HIV healthcare-provider or methadone provider but by independent researchers outside these settings, who are less likely to elicit socially desirable answers. Furthermore, we showed that, when adherent, active drug users in the no/incomplete HR group can achieve similar viral load suppression as less active or former drug users in the less dependence on HR group (see Table 2). Important factors such as time on HAART or nadir CD4 count were not taken into account though. Finally, we cannot exclude selection bias. The participation of the patients in our cohort may indicate that they are more aware of their health compared to patients not participating in the cohort.

In conclusion, this study suggests that HIV-positive injecting drug users participating in a harm reduction programme can be at least as adherent to HIV treatment as non-injecting drug users with no dependence on harm reduction. Furthermore, it appears to be important for non-injecting drug users less dependent on methadone to continue participation in a harm reduction programme, with specifically a sufficient methadone dosage, to keep them adherent to HAART. This study stresses the importance of offering all drug users systematic and comprehensive care [34-36], in which substance abuse treatment, psychiatric treatment, and social support are integrated. The integration of HIV care within such a system is likely to increase both HAART uptake and adherence. Finally, our findings suggest that when comprehensive harm reduction programmes are implemented in settings with a high prevalence of injecting drug users, such as Eastern-Europe or Asia, access to HAART can and should also be increased for this specific population.

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Chapter 2.2

Hepatitis C testing and treatment among active drug users in Amsterdam: results from the DUTCH-C project

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Abstract

Background

Although hepatitis C virus (HCV) treatment has shown to be effective, uptake of treatment among active drug users is still low. The Drug Users Treatment for Chronic Hepatitis-C project aims to offer active drug users in Amsterdam HCV testing and treatment using a multidisciplinary approach.

Methods

The study population comprises drug users participating in the Amsterdam Cohort Studies and drug users referred to the Drug Users Treatment for Chronic Hepatitis-C unit. Drug users were offered HCV testing and, if chronically infected, medical and psychiatric screening and HCV treatment. Various specialists collaborated to provide optimal care. We assessed test-uptake and treatment-uptake and outcomes.

Results

Four hundred and ninety-seven Amsterdam Cohort Studies drug users were offered HCV testing: 449 out of 497 (90%) accepted. HCV antibodies were found in 267 out of 449 (60%): 183 out of 267 (69%) were HCV-viremic and 49 out of 183 (27%) were HIV-co-infected. Of the 134 HCV-monoinfected patients, 102 (76%) initiated additional medical screening and 44 started treatment by 1 July 2009. Sixty-two drug users referred from methadone clinics were also HCV-monoinfected, of whom 14 started treatment by 1 July 2009. In total 58 persons were treated: 16 (27%) with genotype 1 or 4, 42 (72%) with genotype 2 or 3. Eighty-four percent used methadone, 97% used drugs (heroin, cocaine or amphetamine) at least once in the 6 months before treatment, 19% were active injectors. Sixty-two percent used alcohol, 41% had psychiatric disease other than substance abuse. Of the 57 individuals with sufficient follow-up, 37 (65%) achieved sustained virological response.

Conclusion

In a multidisciplinary setting, HIV-negative drug users with chronic HCV infection can be treated successfully despite active drug or alcohol use and psychiatric diseases. Therefore, access to HCV therapy using an integrated approach should be increased for this population.

Introduction

Globally, an estimated 170 million people are infected with the hepatitis C virus (HCV). Chronic HCV infection can cause cirrhosis, liver carcinoma, and liver failure. Specifically, former and active injecting drug users (DU) are at high risk of HCV infection, with HCV prevalence ranging from 50 to 95% [1]. Standard treatment with pegylated interferon and ribavirin is available since 2001, with an overall sustained virological response (SVR = HCV RNA-negative 24 weeks after end of treatment) rate of about 60% [2, 3].

However, active DU, injecting and noninjecting, are less likely to be treated for HCV infection than other populations [4, 5]. In some countries illicit drug use still remains an exclusion criterion for HCV treatment. Reasons for DU not to access HCV treatment include their general lack of access to health care and insufficient HCV-related knowledge. In addition, physicians' reluctance to prescribe treatment is a considerable barrier [6]. The complex lifestyle and condition of DU leave physicians in doubt whether to start treatment, which needs high adherence for efficacy and can cause serious side-effects. Particularly the psychiatric effects, such as depression and suicidal ideation, are problematic in these already vulnerable patients. Another impediment to starting treatment is possible HCV reinfection because of the ongoing injections.

Treatment of HCV infection among DU can achieve success comparable with treatment in nondrug using populations, with SVR ranging from 28 to 94%, depending on HCV genotype [7-22]. However, most studies are small and/or performed in facilities that do not permit active drug use during treatment. Therefore, larger studies with more flexible permissive settings and prolonged follow-up are needed to find an optimal HCV treatment-strategy for active DU [22-24].

In December 2004, we started the Drug Users Treatment for Chronic Hepatitis-C (DUTCH-C) project. This project aimed to offer HCV screening and treatment to all DU participating in the Amsterdam Cohort Study (ACS) [25] at the Public Health Service Amsterdam (PHSA) and to develop guidelines for HCV treatment of active DU outside a clinical setting. Our population consisted of active and former DU, injecting or not, with a background of psychiatric co-morbidity and social problems such as unstable housing and recurrent incarceration. Here, we present the results of the DUTCH-C project.

Methods

Drug Users Treatment for Chronic Hepatitis-C unit

The ACS among DU is an open, ongoing prospective cohort initiated in 1985. Within the ACS, the DUTCH-C project was started in December 2004 to evaluate the feasibility of HCV testing and treatment in DU. Based on the recommendations in literature [8, 23, 26], a multi-disciplinary unit was established. Collaboration was set up linking ACS medical staff (two physicians, two nurses) with a liver specialist, a psychiatrist, and a virologist from the Amsterdam Medical Center (AMC) and with addiction specialists and case-load managers from methadone clinics. The DUTCH-C treatment unit is located in the PHSA near a major clinic providing methadone and heroin substitution therapy.

HCV treatment is provided by ACS medical staff and the AMC liver specialist. Methadone and all psycho-pharmaceutical medications are prescribed by the addiction specialists and psychiatrists. Care providers from the methadone clinics provide support and observe the development of side-effects. No incentives were offered. The DUTCH-C is part of the ACS among DU, approved for by the medical ethics committee of the AMC and requiring written informed consent for participation.

Study population I

Within the ACS, approximately 500 DU visit the PHSA twice yearly for HIV testing and completion of standardized questionnaires. All DU visiting from December 2004 were offered HCV testing and received counselling on HCV transmission risk and treatment possibilities.

Study population II

On account of the successful testing and treatment results seen in ACS DU, it was decided in 2007 to extend HCV treatment to non-ACS DU, referred from methadone clinics and other addiction clinics in Amsterdam. These DU had either been tested HCV positive before or were considered to have a high likelihood of being infected. Their subsequent testing, counselling, and treatment were identical to that given to ACS participants.

Hepatitis C virus testing

Blood samples were collected and tested for HCV antibodies (AxSym version 3.0; Abbott, Wiesbaden, Germany). When HCV antibodies were found, blood was tested for HCV RNA (TMA Versant, Siemens), HCV load was determined (Siemens Versant bDNA, version 3.0), and genotyping was performed as described by Murphy et al. [27]. Those who were negative for HCV antibodies or positive for antibodies but negative for HCV RNA are offered annual retesting for HCV.

Medical screening to assess HCV treatment eligibility

All HIV-negative participants with detectable HCV RNA were offered additional screening to determine treatment eligibility. Treatment options for HIV-positive participants with chronic HCV are currently being evaluated.

The additional medical screening consisted of physical examination, liver ultrasound, standard chest radiograph, and psychiatric evaluation in the AMC and PHSA. If needed, psychiatric medication was started, after which HCV treatment possibilities were re-evaluated. Addiction specialists were consulted for each patient to discuss social, medical, psychiatric, and abuse-related issues. Each patient's general practitioner was consulted if possible.

DU infected with HCV genotype 1 or 4 were offered a liver biopsy; those with less than moderate fibrosis were advised to postpone the treatment [28] and wait for future options with specifically targeted antiviral therapy against HCV in addition to pegylated interferon and ribavirin [29]. Patients refusing liver biopsy but requesting treatment were allowed to initiate treatment if no exclusion criteria were present.

Criteria for exclusion from treatment

Standard medical exclusion criteria for HCV treatment were used [30], including decompensated liver cirrhosis, cardiac failure, or auto-immune disease. Psychiatric illness, active drug and alcohol use were not considered an exclusion criterion, as long as it did not interfere with scheduled visits and was considered stable by the ACS physician. DU were required to have stable housing and no acute or uncared for juridical or financial impediments.

Hepatitis C virus treatment

HCV treatment was standard for all participants: 24 or 48 weeks of pegylated interferon α 2a or 2b and ribavirin for HCV genotypes 2 and 3, and 1 and 4, respectively. Dosages were according to the standard of care and individually adjusted based on side-effects. DU attended the DUTCH-C unit once weekly for pegylated interferon administration and complete check-up by either the physician or nurse. Psychiatric screening was conducted at week 0, 4 and 8 of treatment using the Beck Depression Index and the Hospital Anxiety and Depression Scale. Anytime during treatment, the patients could be referred to other care providers. Ribavirin was distributed at methadone clinics, shelters, or the DUTCH-C unit. Frequency of distribution differed per individual and matched methadone distribution if applicable.

Data collection

For ACS participants (study population I), self-reported data on acceptance of HCV testing, prior HCV testing and treatment, socio-demographic, medical and psychiatric characteristics and drug use and alcohol use (type/method/quantity/frequency) were collected during testing, at the beginning of treatment ($t = 0$) and systematically during treatment. For non-ACS participants (study population II), these data were collected at the beginning of and during treatment. Blood and standardized questionnaires were collected regularly during treatment, evaluating treatment response, (psychiatric) side-effects, drug use and alcohol use, and ribavirin compliance.

Statistical analysis

Analyses were restricted to persons tested before 1 July 2009 and if applicable medically screened and started with treatment before 1 July 2009. Treatment results are given as known by 1 September 2010.

First, we tested ACS participants for differences in characteristics between those accepting and those refusing HCV testing. Second, we tested for differences between those accepting and completing and those refusing or not completing medical screening. Third, we tested treated ACS participants and non-ACS participants for differences in characteristics between those with SVR and those without SVR.

Univariate analysis was performed using Pearson's w^2-test, Student's *t*-test or Mann–Whitney *U* test. General characteristics tested for in univariate analysis included homelessness, methadone use and HCV treatment history (Tables 1 and 3). Drug use characteristics tested included history of injecting drugs and drug use in the last 6 months, specified to type, manner and frequency of drug use (Tables 2 and 4).

All variables with $P < 0.10$ in univariate analysis were considered in a multivariate logistic regression model using backward selection. Multivariate analysis was only performed regarding HCV testing acceptance, since for acceptance of medical screening and for HCV treatment outcome numbers were small. In the multivariate model, testing for differences in HCV testing acceptance, we included the following determinants: alcohol use, homelessness, using methadone on prescription and HCV treatment history. $P < 0.05$ was considered to be statistically significant. SPSS 17.01 (Statistical Package for Social Sciences) was used for all analyses.

Results

Study population

Figure 1 presents the flow chart of HCV testing, medical screening, and treatment.

Between January 2005 and April 2007, 497 DU from the ACS were offered HCV testing (study population I). From 2007 onwards, non-ACS DU referred from methadone clinics and other addiction clinics were also eligible for HCV testing and treatment (study population II). Between 2007 and July 2009 81 persons were referred. General and drug use characteristics of ACS participants offered testing are shown in Tables 1 and 2. As the patients from study population II did not fill out questionnaires during HCV testing, comparison of characteristics with population I is not possible.

HCV testing: uptake and results

Testing for HCV was accepted by 90% (449 out of 497) of ACS DU of whom 15% (66 out of 449) were HIV-infected. In multivariate analysis, those reporting previous HCV treatment significantly more often refused HCV testing [odds ratio (OR): adj = 0.2; 95% confidence interval (CI): 0.06–0.59]. DU using prescribed methadone and DU not being homeless significantly more often accepted HCV testing (OR: adj = 2.3; 95% CI: 1.22–4.40 and OR: adj = 2.8; CI: 95% = 1.17–6.71).

Almost 60% of DU (267 out of 449) tested positive for HCV antibodies; with a prevalence of 54% in HIV-negative participants and 89% in HIV-infected participants. Of the HCV antibody positive HIV-negative participants 64% (134 out of 208) tested positive for HCV RNA. Overall, screening revealed chronic HCV infection in 35% (134 out of 383) of HIV-negative participants and 74% (49 out of 66) of HIV-positive participants.

Of the 81 DU referred from methadone and addiction clinics (study population II), 79 (98%) were tested, 73 out of 79 (92%) were RNA positive, of whom 62 (85%) were HCV monoinfected.

Medical screening: uptake and results

Of the 134 HIV-negative ACS DU with chronic HCV infection, 76% (102 out of 134) agreed to additional medical and psychiatric screening; 15 refused, and 17 were either uninsured or lost to follow-up. Reasons for refusing additional screening were diverse, such as homelessness, social problems, fear for therapy, and side-effects. In univariate analysis, injecting drug use in the last 6 months was the only characteristic significantly associated with refusing or not completing medical screening (p= 0.014).

Of those who agreed to screening, 84 completed it, and 18 still needed to complete the process by July 2009. Of the 84 who completed, 24 were not eligible for HCV treatment: eight could not start treatment because of medical, social, or psychiatric contraindication, and treatment was postponed for an additional 16 with genotype 1 or 4 with findings of less than moderate fibrosis in liver biopsy.

Of the 62 HCV-monoinfected DU from study population II, 56 (90%) initiated medical screening, of whom 10 still needed to complete screening by July 2009, seven refused

to complete the screening or were lost to follow-up and 39 completed the screening. Twenty-three out of 39 (59%) were not eligible for treatment, because of medical or social contraindications (six out of 39) or postponement of treatment because of less than moderate fibrosis (17 out of 39).

HCV treatment uptake

Of the 60 ACS DU eligible for treatment, 27% (16 out of 60) refused. Reasons for refusing treatment were: fear of therapy and side-effects (*n* = 4), social problems (*n* = 2), co-morbidity (*n* = 3), being lost to follow-up (*n* = 4) and unknown (*n* = 3). The 73% (44 out of 60) who started treatment represented 33% (44 out of 134) of all HIV-negative participants with chronic HCV. We extended our data with 14 non-ACS DU eligible for and accepting treatment (study population II), resulting in 58 patients starting HCV treatment before July 2009.

The median time between HCV testing and HCV treatment initiation was 17 months (interquartile range 10-28 months).

Characteristics at HCV treatment initiation

Characteristics at treatment initiation of the HCV-treated group are presented in Tables 3 and 4. In the 6 months before treatment initiation, 97% (56 out of 58) used illicit drugs (heroin/cocaine/amphetamines non- injecting and/or injecting); 19% (11 out of 58) injected drugs (heroin/cocaine/amphetamines); 62% (36 out of 58) used alcohol, and 84% (49 out of 58) used prescribed methadone.

A Diagnostic and Statistical Manual of Mental Disorders psychiatric diagnosis (not including substance abuse) was diagnosed in 41% (24 out of 58), of whom nine were diagnosed with a mood and/or anxiety disorder and eight with a psychotic disorder. Overall, 47% (27 out of 58) of participants started HCV treatment with prescribed use of psycho-pharmaceutical medication.

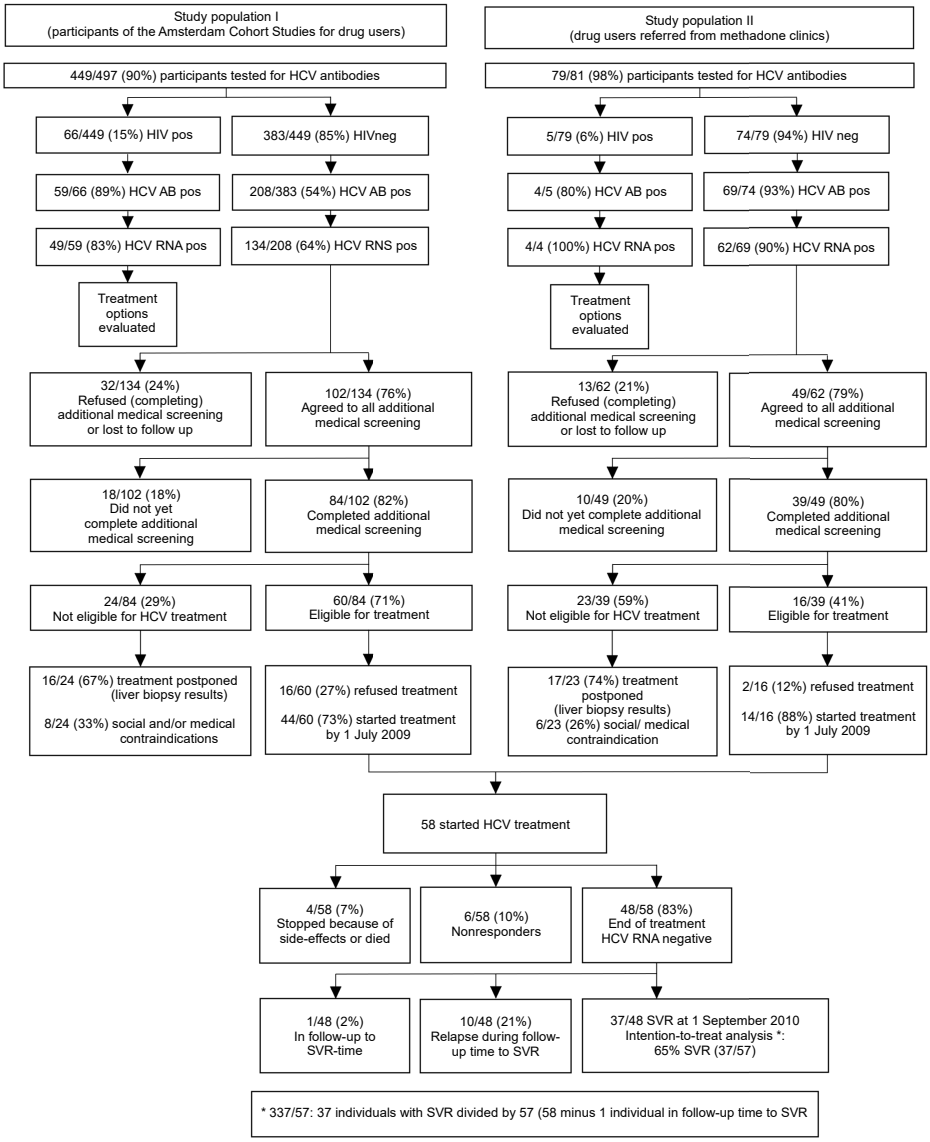

Figure 1. Overview of participation and HCV test and treatment outcomes in the DUTCH-C Project. *35/57: 37 individuals with sustained virological response (SVR) divided by 57 (58 minus one individual in follow-up time to sustained virological response). HCV, hepatitis C virus; Neg, negative.

Table 1. Characteristics of participants of the Amsterdam Cohort Studies offered Hepatitis C virus testing from January 2005 to July 2009.

General characteristics	ACS participants offered HCV testing, N=497 (%)
Age (mean)	43.9 years; STD 7.6 years
Sex	
Male	342/497 (68.8)
Nationality	
Dutch	413/497 (83.1)
Years of education after 12th year (median)	4.0 years; IQR 3-6 years
Homeless	
Yes	41/497 (8.2)
HIV-sero-positivity	
Yes	71/497 (14.3)
Methadone use on prescription	
Yes	379/497 (76.3)
Ever treated before for HCV	
No (not HCV-infected or HCV-status not known)	443/488 (90.8)
No treatment, but regular check-up by HCV specialist	27/488 (5.6)
Yes, treatment by HCV-specialist	15/488 (3.1)
	SVR = 33% (5/15)

ACS, Amsterdam Cohort Study; HCV, hepatitis C virus; IQR, Inter quartile range; SD, standard deviation; SVR, sustained virological response.

Table 2. Drug use characteristics of participants of the Amsterdam Cohort Studies offered hepatitis C virus testing from January 2005 to July 2009.

Drug use characteristics	ACS participants offered HCV testing, N= 497 (%)
Ever injected drugs	
Yes	335/497 (67.4)
Drug use (injecting and/or noninjecting) in last 6 months	
Yes	418/497 (84.1)
Noninjecting drug use (heroin/cocaine/amphetamines)	
in last 6 months	
Yes	404/486 (83.1)

Table 2. Continued.

Drug use characteristics	ACS participants offered HCV testing, N= 497 (%)
Noninjecting heroin use in last 6 months	
No	239/497 (48.1)
One-several times per day	59/497 (11.9)
Several days per week	78/497 (15.7)
One day per week	27/497 (5.4)
Several days per month	21/497 (4.2)
One day or less than one day per month	54/497 (10.9)
Unkown	19/497 (3.8)
Noninjecting cocaine use in last 6 months	
No	490/497 (98.6)
Several times per day	1/497 (0.2)
Several days per week	2/497 (0.4)
One day per week	3/497 (0.6)
Several days per month	0
One day per month	1/497 (0.2)
Noninjecting amphetamine use in last 6 months	
No	476/497 (95.8)
One time per day	1/497 (0.2)
Several days per week	4/497 (0.8)
One day per week	1/497 (0.2)
Several days per month	2/497 (0.4)
Less than one day per month	10/497 (2.0)
Injecting DU in last 6 months	
Yes	92/335 (27.5)
Injecting heroine use in last 6 months	
No	453/497 (91.1)
Once-several times per day	14/497 (2.8)
Several days per week	3/497 (0.6)
One day per week	1/497 (0.2)
Several days per month	6/497 (1.2)
One day or less than one day per month	18/497 (3.6)
Unknown	2/497 (0.4)

Table 2. Continued.

Drug use characteristics	ACS participants offered HCV testing, N= 497 (%)
Injecting cocaine use in last 6 months	
No	469/497 (94.4)
Several times per day	1/497 (0.2)
Several days per week	7/497 (1.4)
One day per week	1/497 (0.2)
Several days per month	2/497 (0.4)
One day or less than one day per month	16/497 (3.2)
Unknown	1/497 (0.2)
Injecting amphetamine use in last 6 months	
No	480/497 (96.6)
Several times per day	1/497 (0.2)
Several days per week	4/497 (0.8)
One day per week	3/497 (0.6)
Several days per month	0
One day or less than one day per month	9/497 (1.8)
Alcohol use in last 6 months	
Yes	261/497 (52.5)

ACS, Amsterdam Cohort Study; HCV, hepatitis C virus

Table 3. Characteristics at treatment initiation of participants of the DUTCH-C project that started HCV treatment.

Characteristics	Participants initiating treatment N=58 (%)
Age (mean)	47.7 years; SD 5.5 years
Sex	
Male	43/58 (77.1)
Nationality	
Dutch	36/58 (62.1)

Table 3. Continued.

Characteristics	Participants initiating treatment N=58 (%)
Genotype	
Genotype 1	13/58 (22.4)
Genotype 2	11/58 (19.0)
Genotype 3	31/58 (53.4)
Genotype 4	3/58 (5.2)
Homeless	
Yes	1/58 (1.7)
Methadone on prescription	49/58 (84.4)
Median dose in milligrams per day	80.0; IQR 50-100
Psychiatric diagnosis, other than substance abuse	
Yes	24/58 (41.4)
Personality disorder	7/58 (12.1)
Depression	5/58 (8.6)
Psychotic disorder	8/58 (13.8)
Personality disorder, and depression	2/58 (3.4)
Personality disorder, and anxiety disorder	2/58 (3.4)
Psychopharmacological medication	
Yes	27/58 (46.6)
Antidepressants	7/58 (12.1)
Benzodiazepines (BD)	11/58 (19.0)
Antipsychotics (AP)	5/58 (8.6)
Antidepressants + BD	1/58 (1.7)
Antidepressants + AP	2/58 (3.4)
Antipsychotics + BD	1/58 (1.7)

DUTCH-C, Drug Users Treatment for Chronic Hepatitis-C; HCV, hepatitis C virus; IQR, inter quartile range; SD, standard deviation

Table 4. Drug use characteristics at treatment initiation of participants of the DUTCH-C project that started HCV treatment.

Drug use characteristics	Participants initiating treatment N=58 (%)
Ever injected drugs	
Yes	51/58 (87.9)
Drug use (injecting and/or noninjecting) in last 6 months	
Yes	56/58 (96.6)
Noninjecting heroin use in last 6 months	
Yes	31/58 (53.4)
Median number of days in last 6 months	1.0; IQR 0.0-7.0
Less than 1 day per week	13/31 (41.9)
One or two days per week	4/31 (12.9)
Three or four days per week	6/31 (19.3)
Seven days per week	8/31 (25.8)
Median grams per time	0.5; IQR 0.2-0.9
Noninjecting cocaine use in last 6 months	
Yes	38/58 (65.5)
Median number of days in last 6 months	1.0; IQR 0.0-3.0
Less than one day per week	14/38 (36.8)
One or two days per week	12/38 (31.6)
Three days per week	6/38 (15.8)
Seven days per week	6/38 (15.8)
Median grams per time	0.4; IQR 0.3-0.5
Noninjecting amphetamine use in last 6 months	
Yes	1/58 (1.7)
Injecting DU in last 6 months	
Yes	11/58 (19.0)
Injecting heroine use in last 6 months	
Yes	11/58 (19.0)
Median number of days in last 6 months	1.0; IQR 0.0-6.0
Less than one day per week	4/11 (36.4)
One or two days per week	3/11 (27.3)
Four days per week	1/11 (9.1)
Six or seven days per week	1/11 (27.3)*
Median grams per time	0.5; IQR 0.1-0.5

Table 4. Continued.

Drug use characteristics	Participants initiating treatment N=58 (%)
Injecting cocaine use in last 6 months	
Yes	5/58 (8.6)
Median number of days in last 6 months	0.0 ; IQR 0.0-3.5
Less than 1 day per week	3/5 (60)
One day per week	1/5 (20)
Six days per week	1/5 (20)
Median grams per time	0.1; IQR 0.1-0.1
Alcohol use since previous visit (last 6 months)	
Yes	36/58 (62.1)
Median alcohol consumption in grams per day	10; IQR 0-48

DUTCH-C, Drug Users Treatment for Chronic Hepatitis-C; DU, drus users; HCV, Hepatitis C virus; IQR, Inter quartile range

*erratum in original article: should be 9.1

HCV treatment results and course

By 1 September 2010, 48 out of 58 (83%) reached the end of treatment and all were found HCV RNA-negative (see Fig. 1). Side-effects discouraged three to continue treatment, and one died of a cause unrelated to HCV-therapy (lymphoma). Virological nonresponse at week 12 was seen in six patients, whose treatment was then stopped according to the Dutch national HCV treatment guidelines [28]. After being HCV RNA-negative at end of treatment, 10 out of 48 patients relapsed early (within 24 weeks post-treatment); 37 out of 48 reached SVR and were thus successfully treated. For one patient, follow-up was still insufficient to reach SVR.

Overall, in intention-to-treat analysis, SVR was reached by 65% (37 out of 57) of patients with sufficient follow-up time, with 76% (31 out of 41) reaching SVR in those with genotype 2 or 3, and 38% (six out of 16) reaching SVR in those with genotype 1 or 4. Univariate analysis showed that having genotype 2 or 3 was significantly associated with SVR compared to having genotype 1 or 4 (OR = 5.2; 95% CI: 1.5–17.8). The associations between age and SVR, and methadone use on prescription and SVR, were borderline significant, with successfully treated patients tending to be younger ($P = 0.08$) and more often using methadone ($P = 0.09$). There were only two persons that had not used drugs in the 6 months before treatment and both showed SVR as treatment outcome. When comparing manner of drug use, we did

not find a difference in outcome between those injecting and those not injecting (OR: 1.07; 95% CI: 0.27–4.2).
Patients attended more than 95% of scheduled visits (either the same day or the next day after being reminded) at which peg-interferon was injected. One patient was incarcerated during treatment and one patient had to be admitted to an addiction clinic because of excess cocaine use, but for both the patients treatment was always continued. Amounts of drug use during treatment were collected systematically and will be evaluated (data not shown). Treatment was never interrupted or stopped because of psychiatric events. Less than 10% of patients needed the start of antidepressants during treatment. Five patients suffered from (recurrent) pneumonia. All were treated with antibiotics and this co-morbidity was never a reason to stop HCV treatment.

Discussion

With the DUTCH-C project, we showed that HCV testing and HCV treatment uptake and response among active injecting and noninjecting DU with chronic HCV infection and psychiatric co-morbidity can approach up-take and response in the nondrug using population.
The willingness of our population to be tested was high. Receiving methadone positively influenced uptake of testing, as described earlier [31]. Homeless DU more often refused testing suggesting that they consider HCV treatment not compatible with their unstable situation. Supporting these specific DU in obtaining proper housing or shelter, may lead to testing acceptance and treatment uptake.
Our population was also willing to start further medical screening, with 63% completing this extensive process. This high willingness may be due to repeated and extensive counselling and familiarity with the DUTCH-C physicians and nurses.
The final uptake by 73% of those eligible for treatment was high. Compared to another study, in which 1.1% (15 out of 1360) of all HCV antibody positive participants started treatment, overall treatment uptake in our study was good (44 out of 267 = 16%) [32]. Uptake is influenced by knowledge about HCV treatment and its side-effects [33]. Although we could not evaluate HCV knowledge, the high uptake in this study might again be explained by extensive counselling, involving families and shelter personnel.
A physician-related barrier to treatment initiation in DU is fear of psychiatric decompensation during treatment. However, our study confirms that treated and stable psychiatric illness does not interfere with HCV treatment success [34-36]. Preventive antidepressants for DU initiating treatment are recommended by some [37, 38]. Our findings do not necessarily support this strategy, with 17% of individuals on antidepressants at HCV treatment initiation

and less than 10% starting antidepressants during treatment. Frequent psychiatric evaluation and support resulted in psychiatric stability among the treated DU.

Primary challenges during HCV treatment among DU are adherence, the influence of drug and alcohol use and coping with adverse side-effects. In the DUTCH-C the majority of participants were active DU, and compliance of weekly visits for peg-interferon injections was excellent. We found that DU can be treated successfully for HCV, despite active drug use, as shown earlier [36]. Likewise, active alcohol use was no barrier to starting and succeeding at HCV treatment. Additionally, the use of peer support groups and directly observed therapy of ribavirin may improve the adherence rates and treatment outcome even more [20, 39].

Almost all the adverse side-effects were resolved with dose reduction of peg-interferon or ribavirin, nutritional supplements and extensive counselling. Weekly patient appointments and frequent contact with other care providers enabled us to diagnose and address side-effects early. Only three individuals stopped treatment prematurely, for reasons of unbearable side-effects or social reasons.

Overall, the SVR rate of 65% was comparable with that seen in nondrug using populations (54–63%), especially for DU with genotypes 2 and 3 [2, 3, 40, 41]. The SVR rate in the DUTCH-C project was much higher than the reported SVR rate among ACS participants treated in the hospital before the DUTCH-C project (65% vs. 33%) (see Table 1), a finding that supports the idea that a multidisciplinary approach is effective. Participants with genotypes 1 and 4 showed a relatively low response rate, which might be partly explained by early dropout caused by side-effects. Earlier studies (mentioned in the introduction section), mainly among opioid-substitution-treated DU, showed moderate-to-good overall response rates (28–94%). When comparing these results with ours, size and characteristics of study population, such as genotype, level of drug use and type of substitution treatment, must be considered.

Studies on HCV reinfection after spontaneous clearance or treatment among injecting DU offer conflicting results [42-48]. In the ACS, injecting and related risk behaviour, such as sharing needles, has considerably declined over the years [49]. In Amsterdam, comprehensive needle exchange and methadone substitution programmes have substantially contributed to a decrease in HCV transmission [50, 51]. Therefore, in the current situation, HCV reinfection after successful treatment is expected to be low.

The study is observational and the lack of randomization and a control group makes it difficult to draw definite conclusions on the effectiveness of our programme. Furthermore, both in uptake of testing and treatment, refusal of participants may have led to selection of more adherent and psycho-socially stable patients. Still, percentages of drug use and psychiatric diagnoses in the treated group are high and indicate that complicated patients can be treated. Data collection of characteristics such as substance abuse is self-reported and may therefore be subject to bias. As the DU were notified that drug use was no exclusion criterion for testing or treatment we expect that the use of self-report in this population is acceptable.

For this study only HIV-negative persons were included. As co-infection of HIV and HCV is particularly concurrent in injecting DU it is of great importance that this difficult to reach population is included in future treatment studies.
Finally, although the proportion of patients that were eligible for treatment and also initiated treatment was substantial, there is still a substantial number of patients who did not start treatment. This is partly because of better treatment options in the nearby future for patients with genotype 1, particularly in study population II. Reasons for patient-related lack in uptake are differential and it may be difficult to further improve uptake.
In conclusion, by careful consideration of potential barriers to HCV screening and treatment, we have developed a successful multidisciplinary approach for the treatment of chronic HCV in former and active injecting and non-injecting DU. In this HCV treatment unit, specialists work closely together for intense coordination of each patient's care. To organize such a unit requires sufficient time, resources, commitment and a flexible attitude towards all issues surrounding individual patients. All social, medical, psychiatric and abuse-related issues should be taken into account by an HCV-specialist experienced in treating DU, before an individual decision on treatment initiation can be taken. Although some standard exclusion criteria are valid for this group, the complexity of this population does not allow the development and use of strict HCV treatment (initiation) protocols. With this approach we demonstrated that active drug or alcohol use with or without stable psychiatric co-morbidity, need not interfere with good uptake of HCV treatment and good treatment results.

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Chapter 3

Incidence and treatment of HCV infection among HIV-infected MSM

Chapter 3.1

Stabilizing incidence of hepatitis C virus infection among men who have sex with men in Amsterdam

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Introduction

Since 2000, there has been an unexpected and substantial increase in the incidence of hepatitis C virus (HCV) among HIV-1-infected men who have sex with men (MSM) [1-3]. Prevalence of HCV among HIV-uninfected MSM has remained low [1]. HIV may enhance sexual transmission of HCV through increased infectiousness and increased susceptibility [1-3]. In combination with increased high-risk sexual behavior, these factors most likely allowed HCV to spread sexually [1-3]. The Multicenter AIDS Cohort Study (MACS) in the United States reported significantly higher HCV incidence rates (IRs) among MSM recruited in 2001-2003 compared with earlier periods [4]. Studies from Switzerland, Spain, and Japan showed an ongoing increase in new HCV infections among HIV-infected MSM from 2008 till 2011/2012 [5-7]. In contrast, data collected during bi-annual surveys at the sexually transmitted infection clinic in Amsterdam, the Netherlands, suggested that the prevalence of HCV among HIV-infected MSM has stabilized in recent years [8]. We therefore updated our previous analysis in the Amsterdam Cohort Study (ACS) among MSM [9] to examine recent changes in HCV incidence.

Methods

Participants

The ACS among MSM is an open, ongoing prospective study initiated in 1984 [10]. Participation is voluntary and informed consent is obtained at intake. Participants return every 3-6 months for follow-up. Since 1999, the follow-up of nearly all HIV-infected MSM has been relocated to HIV treatment centers, where collection of behavioral data is limited. We included all HIV-infected and HIV-uninfected MSM with ≥2 study visits between October 1984 and January 2012. HCV status of each participant up to January 2003 has been retrospectively determined as described previously [9]. New participants since 2003, and HIV-uninfected MSM with a negative HCV status who have remained in follow-up, were (again) tested for HCV antibodies at their first visit after October 2008. To update the HCV status among HIV-infected MSM with a negative HCV status in our previous study, we obtained all available HCV screening results from the clinical records of HIV treatment centers attended by ACS participants. If no test result was available after January 2009, the last available sample before January 2012 was tested for HCV antibodies. On finding incident HCV infection, samples from earlier visits were tested to minimize width of seroconversion interval.

Laboratory methods

HCV antibody testing was performed using a commercial microparticle enzyme immunoassay (AxSYM®HCV 3.0; Abbott Laboratories, Abbott Park, IL, USA) and confirmed by immunoblot (Chiron RIBA HCV 3.0 SIA; Ortho-Clinical Diagnostics, Raritan, NJ, USA) and transcription-mediated amplification (TMA Versant; Siemens Medical Solutions Diagnostics, Tarrytown, NY, USA).

Statistical analysis

Participants contributed follow-up time from the date of study entry until the date of the last negative HCV antibody test, or until the estimated date of HCV infection (i.e., the midpoint between the last negative and the first positive HCV test). IRs were calculated per year, and trends over time were analyzed using Poisson regression. Restricted cubic splines allowed for smoothly varying trends in the modeled incidence [11]. In a bivariate analysis for incident HCV infection among HIV-infected MSM, adjusting for calendar period of follow-up, the effects of age, CD4 cell count, nadir CD4 cell count, HIV viral load (modeled as log10 increment above 1000 copies/mL), and combination antiretroviral therapy (cART) use were evaluated using Poisson regression. Variables subject to change were treated as time-updated covariates. Statistical software packages STATA Intercooled 11.2 (StataCorp, College Station, TX, USA) and R 2.15.2 [12] were used for analysis.

Results

The ACS enrolled 2457 MSM between October 1984 and January 2012, of whom 2104 had ≥2 study visits and HCV test results. Median age of the 2104 MSM at study entry was 30.3 years (interquartile range, IQR: 25.9-37.1) and 78.8% had Dutch nationality. At study entry, 539 (25.6%) of 2104 MSM were HIV infected; an additional 222 MSM seroconverted during follow-up. At study entry, 2080 of 2104 MSM were HCV negative and contributed to 17,310 person-years (PYs) of follow-up; median follow-up time was 7.4 years (IQR: 3.2-12.0). Of the 422 HIV-infected MSM followed up after 1996, 345 were ever on cART.

Twenty-nine incident HCV infections were documented during the observation period. All incident cases were infected with HIV before HCV infection and none of them reported injection drug use (IDU) at study entry. Based on 6422 PYs of follow-up among HIV-infected MSM, the overall observed HCV incidence was 4.52/1000 PYs [95% confidence interval (CI): 3.02-6.49]; the effect of calendar time was significant (P<0.001). Before 2000, only 3 incident HCV infections were documented, resulting in an IR varying between 0.73 and 3.60/1000 PYs (Fig. 1A). A significant increase in HCV incidence was observed after 2000 (IR_{2005} vs. IR_{2000}: IRR,

3.41; 95% CI: 1.58 to 7.34; *P*=.002). After 2005, however, HCV incidence stabilized at around 12/1000 PYs (IR_{2010} vs. IR_{2005}: IRR, 0.94; 95% AU2 CI: 0.38-2.36; *P*=.906).

In Poisson regression, younger age was associated with incident HCV infection (age 50 vs. 35 years: RR, 0.31; 95% CI: 0.11-0.89; *P*=.041; Fig. 1B). Of the other evaluated risk factors, none were significantly associated with HCV infection after adjusting for calendar year: CD4 count (800 vs. 300 cells/mL: RR, 0.96; 95% CI: 0.33 to 2.79), nadir CD4 count (300 vs. 150 cells/mL: RR, 1.09; 95% CI: 0.46 to 2.58), HIV viral load (30,000 vs. 1,000 copies/mL: RR, 2.27; 95% CI: 0.82 to 6.29), and cART use (RR: 0.80, 95% CI: 0.34 to 1.88).

Infections were mostly of genotype 1 (14/29; 48.3%), followed by genotype 4 (7/29; 24.1%), in line with our previous study [9]. Infection with genotype 2b (N=3) was observed after 2008 only and might indicate the introduction of a new HCV genotype among HIV-infected MSM in the Netherlands. No statistically significant time trend in genotype distribution was found.

Discussion

We describe incidence of HCV infection among MSM in Amsterdam over the course of almost 3 decades. HCV incidence rose sharply among HIV-infected MSM between the years 2000 and 2005 but seems to have stabilized at a higher level of around 12/1000 PYs thereafter, although CIs were wider in the years 2005-2011. Our observation of stabilizing incidence corresponds with findings from the Amsterdam sexually transmitted infection clinic and may partly result from increased HCV testing and treatment uptake and increased HCV awareness leading to a reduction of risk behavior and a saturation effect in the group at highest risk for HCV infection [8]. No incident HCV infections were documented among HIV-uninfected MSM, despite more than 10,000 PYs of follow-up, which supports earlier findings that HCV mainly spreads among HIV-infected MSM [1, 3]. Sexual transmission of HCV has occurred among a few HIV-uninfected MSM [1].

Our findings show a leveling off in HCV incidence among HIV-infected MSM rather than an ongoing increase, in contrast to studies from Switzerland, Spain, Japan, and the United States [4-7]. However, the HCV epidemic and the subsequent public health response among MSM in the Netherlands may have started earlier.

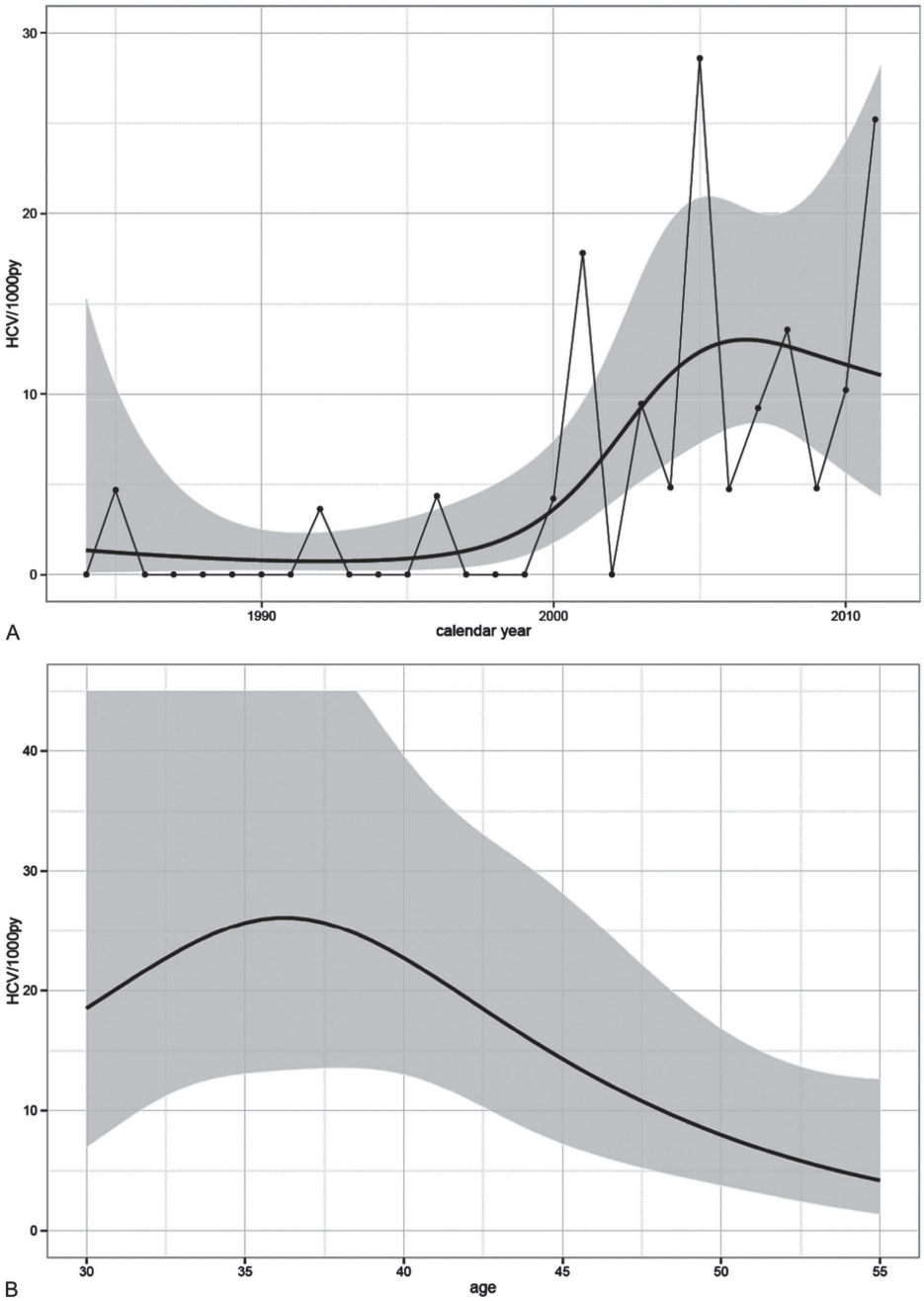

Figure 1. Observed and fitted HCV IR per 1000 PYs of follow-up. A, HCV IR among 761 HIV-infected MSM participating in the Amsterdam Cohort Studies, 1984–2011. The shaded area is the 95% CI.
B, HCV IR by age, among HIV-infected MSM participating in the Amsterdam Cohort Studies (in 2008). The shaded area is the 95% CI.

The HCV epidemic in the MACS cohort (with 4 study sites across the United States) seems to differ from the epidemic in the Netherlands [4]. Continuous incident infections have occurred from the mid-80s onwards, with majority of infections (i.e., 67/92; 73%) during the period 1985-1995 among both HIV-infected and HIV-uninfected MSM. The incident HCV infections in these early years might be attributed to IDU (reported by 5%) and blood transfusion (reported by 3%). Besides, the majority of MSM with incident HCV infection (i.e., 67/115; 58%) reported only 1 anal sex partner, suggesting transmission routes other than sexual contact play a major part. The actual outbreak of sexually transmitted HCV may have started later on, but unfortunately, the authors do not differentiate sexually acquired and nonsexually acquired HCV infections over time.
Also study design and methods differ between the MACS and ACS and could partly explain differences in trends. The MACS is a closed cohort with 3 separate enrolment periods, whereas the ACS has inclusion throughout the study period. In contrast to the ACS, in the MACS, 22 MSM with possible incident HCV infection tested HCV antibody positive for the first time at their last study visit were classified as HCV-free, as the MACS definition required 2 consecutive positive visits [4]. In addition, HCV seroconverters with a wide seroconversion interval (≥4 years) were excluded.

Since the start of the HCV epidemic among HIV-infected MSM, multiple HCV genotypes have been introduced and continued to circulate in this population. Because of the relatively few incident infections in our study, we had limited power to test for trends in HCV genotype distribution over time. Genotype 2b is known to be transmitted mainly through invasive procedures, blood transfusion, and IDU [13], but the current spread among MSM is most likely through sexual transmission [14].

The initial scope of the ACS was to study the HIV epidemic; hence data on risk factors for HCV were limited. In addition, data on sexual risk behavior were limited after 1999 as described in our Methods section. Recently initiated HCV-specific cohort studies among MSM in the Netherlands, the United Kingdom, and Germany will be better able to provide insight into the role of traditional and sexual risk factors for HCV infection and reinfection among MSM [15-17].

In conclusion, the incidence of HCV infection among HIV-infected MSM in Amsterdam seems to have stabilized after an initial increase until 2005. The overall disease burden is likely to remain high because studies in the cART era show that HIV-HCV co-infection results in an increased risk of both HCV and HIV mortality [18-20]. Infected individuals will benefit from the swiftly changing landscape of HCV treatment. Continued follow-up is needed to see if the HCV epidemic among HIV-infected MSM will also stabilize in other regions of the world.

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Chapter 3.2

Alarming incidence of hepatitis C virus re-infection after treatment of sexually acquired acute hepatitis C virus infection in HIV-infected MSM

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Abstract

Background

Recent data indicate that seroprevalence of sexually transmitted hepatitis C virus (HCV) infection among MSM is stabilizing in Amsterdam. However, little is known about the incidence of HCV re-infection in MSM who have cleared their HCV infection. We, therefore, studied the incidence of re-infection in HIV-infected MSM who were HCV RNA-negative following HCV treatment of acute primary infection.

Methods

Our study population comprised HIV-infected MSM at two large HIV out-patient clinics in Amsterdam, who were previously diagnosed with a sexually transmitted acute HCV infection and tested HCV RNA-negative at the end of treatment. We defined HCV re-infection as detectable HCV RNA in individuals with an undetectable HCV RNA at the end of treatment accompanied by a switch in HCV genotype or clade. Person–time methods were used to calculate the incidence of re-infection.

Results

Fifty-six persons who became HCV RNA-negative during primary acute HCV treatment were included. Five of the 56 cases relapsed and were not analysed. Eleven persons were re-infected. The incidence of HCV re-infection in this group was 15.2 per 100 person-years (95% confidence interval 8.0– 26.5). The cumulative incidence was 33% within 2 years.

Discussion

An alarmingly high incidence of HCV re-infection was found in this group. This high re-infection rate indicates that current prevention measures should be discussed, frequent HCV RNA testing should be continued after successful treatment and, in case of possible relapse, clade typing should be performed to exclude re-infection.

Introduction

In the last decade, the sudden increase in incidence of acute hepatitis C virus infection (HCV) among HIV-infected MSM in Europe, Australia and the United States has led to a substantial number of studies on this new public health problem. It has become clear that transmission takes place in specific clusters of HIV-infected MSM engaging in high-risk sexual behaviour [1-3]. Subsequently, targeted prevention messages have been developed, focusing on sexual risk behaviour, recreational drug use and regular testing for HCV. Furthermore, treatment of HCV co-infection in this population has proven to be very successful in the acute phase, and recommendations on treatment have been published [4, 5].

The response to this epidemic has clearly been extensive, and a recent study in Amsterdam has suggested that the prevalence of new primary HCV infections may no longer be increasing (A.T. Urbanus et al., presented at AIDS Conference 2010, abstract WEPDC 104). The question remains, however, whether prevention messaging and early testing and treatment also prevents HCV re-infection in MSM co-infected with HCV and HIV who have cleared their infection.

HCV re-infection occurs frequently among IDUs who continue high-risk behaviour [6]. Incidence rates of re-infection vary depending on population, definition of re- infection and methods and frequency of testing [6-10]. Reports on HCV re-infection by sexual transmission among MSM have been published only rarely [11, 12] (H.-J. Stellbrink et al., presented at CROI 2011, poster 645; presented at International Congress on Drug Therapy in HIV Infection 2010, poster 200; and J. Sasadeusz et al., presented at EASL 2011, poster presentation), and no specific incidence rates have been presented yet.

Therefore, the objective of the current study was to examine the incidence of HCV re-infection among HIV-infected MSM attending two HIV outpatient clinics in Amsterdam, who were HCV RNA-negative at the end of treatment for their initial acute HCV infection.

Methods

Study population

We included 56 HIV-infected MSM at the HIV outpatient clinics of two major hospitals in Amsterdam, who had been previously diagnosed with and treated for an acute HCV infection between 2003 and 2011; none had detectable HCV RNA at the end of their HCV treatment. All patients had been treated with weekly injections of peg-interferon and daily doses of

ribavirin, the majority for a duration of 24 weeks [13]. In the majority of the cases, no HCV parental transmission routes were identified by clinical history and sexual transmission was the most likely mode of transmission.

Data collection

Sociodemographic, clinical and virological data, such as age, use of HAART, CD4 cell counts, HIV RNA levels, levels of alanine aminotransferase (ALT) and genotype of primary HCV infection were collected from medical files. A subset of the MSM at risk of re-infection (n=21) was included in a prospective study of acute infection with HCV in MSM (MSM Observational Study of Acute Infection with hepatitis C, MOSAIC study). For these patients, additional data on risk behaviour are presented. Data collection exists of an extensive self-administered questionnaire regarding classic risk factors for HCV transmission, such as IDU and sexual risk behaviour, collected at baseline and follow-up visits.

Virological testing

All plasma samples available after the end of treatment were tested for HCV RNA with the Siemens VERSANT transcription-mediated amplification (TMA) assay which has a detection limit of 5 IU/ml. Genotyping of the first TMA-positive sample after the end of treatment was performed by amplifying and sequencing a 389 base pair fragment of NS5B, as described by Murphy et al. [14]. If the genotype was similar to that in the treated primary infection, a 573 base pair fragment of E2 including the hypervariable 1 region (HVR1) was amplified and sequenced directly to identify clade shifts and differentiate between relapse or re-infection.

Definition of re-infection and relapse

Re-infection was defined as having detectable HCV RNA following an undetectable level at the end of treatment, with demonstration of the presence of a different genotype compared with primary infection or, if genotype was similar, a different clade compared with primary infection, as indicated by phylogenetic analysis of the E2/HVR1 region. If in the phylogenetic pretreatment and posttreatment sequences from the same viral subtype (e.g. 1a) large genetic distances were present, as indicated by distinct clustering, this was defined as a clade switch and, therefore, as a re-infection with the same viral subtype. Relapse was defined as a positive HCV TMA after a negative HCV TMA at the end of treatment and no genotype or clade switch compared with the primary infection.

Phylogenetic analysis

Sequences were aligned using Clustal X version 2 [15]. Phylogenetic trees were inferred using maximum-likelihood methods, using a Generalized Time Reversible Model with a gamma

distribution of mutations (GTR G) as implemented in MEGA software package version 5 [16]. Bootstrap values were determined from 500 bootstrap resamplings of the original.

Statistical analysis

The incidence rate of re-infection was estimated by dividing the number of re-infections by the total duration of follow-up. The individuals who had relapses were excluded from this calculation. The cumulative incidence was estimated by Kaplan–Meier methods.

In case of re-infection, follow-up time was calculated as the time between the end of treatment and the date of re-infection; the latter was estimated by taking the midpoint between the last negative HCV RNA test and first positive HCV RNA test. If no re-infection occurred, the censor date for follow-up was the date of the last HCV RNA test.

We compared sociodemographic, clinical, virological and behavioural characteristics, including peak ALT levels during follow-up between patients with and without re-infection. Risk behaviour was compared between MSM with and without re-infection for whom risk questionnaires were available. Differences between the two groups were tested with the x2-test or Fisher's exact test for categorical variables and Student's t-test or Mann–Whitney U-test for continuous variables. Analyses were performed using SPSS (version 17.0; SPSS Inc., Chicago, Illinois, USA). The incidence rate and its confidence interval (CI) were calculated with OpenEpi [17] and are given per 100 person-years.

Results

In total, follow-up was obtained for 56 HIV-infected MSM treated for acute HCV infection who were HCV RNA-negative at the end of treatment. Patients were treated between 2003 and 2011. Patient and virological characteristics are shown in Table 1.

Five of the 56 experienced relapse, as evidenced by sequencing of the E2/HVR1 region, and were excluded from the incidence calculations.

According to our definition, 11 of the remaining 51 persons became re-infected. The total follow-up time for the 51 persons was 72.2 years [median 1.3 years, interquartile range (IQR) 0.5–1.6]. The incidence of HCV re-infection was 15.2 per 100 person-years (95% CI 8.0–26.5). Among the 11 individuals with a re-infection, the median time until re-infection was 8.4 months (IQR 3.6–19.2). The majority of re-infected patients switched from genotype 4 to 1.

Table 1. Baseline and follow-up characteristics of hepatitis C virus–HIV-co-infected patients at risk of hepatitis C virus re-infection.

Characteristics	All (N=51), % (n)	Not re-infected (N=40), % (n)	Re-infected (N=11), % (n)
Baseline			
Median age in years (IQR)	44.3 (39.1–48.8)	44.6 (40.7–48.8	42.3 (36.6–49.1)
Genotype primary infection			
Gt 1	69 (35)	73 (29)	55 (6)
Gt 2	2 (1)	3 (1)	-
Gt 3	4 (2)	5 (2)	-
Gt 4	22 (11)	15 (6)	45 (5)
Unknown	4 (2)	5 (2)	-
Median CD4 cell count at end of treatment (cells/µl)	305 (240–403)	300 (240–308)	335 (243–388)
Follow-up			
Total follow-up time in years	72.2	63.0	9.2
Median follow-up time in years (IQR)	1.3 (0.5–1.6)	1.4 (0.5–2.3)	0.7 (0.3–1.6)
Median time between tests in months (IQR)	3.0 (1.9–4.3)	3.0 (2.0–4.5)	2.7 (1.7–4.1)
cART use	75 (38)	73 (29)	82 (9)
Median maximum ALT during follow-up (U/l)	37 (26–63)	34 (25–56)	67 (28–136)
Median CD4 cell count at last HCV RNA-negative visit (not re-infected)/first HCV RNA-positive sample (re-infected) (cells/µl)	450 (400-620)	450 (400-583)	440 (345-675)
Genotype switch at re-infection			
Gt 1 > Gt 4			18 (2)
Gt 4 > Gt 1			36 (4)
Gt 1 > Gt 2			18 (2)
Gt 1 > Gt1, different clade			18 (2)
Gt 4 > Gt 4, different clade			9 (1)

ALT, alanine aminotransferase; cART, combination antiretroviral therapy; HCV, hepatitis C virus; IQR, inter quartile range.

Three persons became re-infected with the same genotype (clade switch). Figure 1 shows the phylogenetic tree of pretreatment and posttreatment E2-HVR1 sequences of these patients together with pretreatment and posttreatment sequences of relapse patients. Pretreatment and posttreatment sequences from patients O1, O2, O3, P06 and P44 clearly cluster together and they were, therefore, classified as 'true' relapsers, corresponding with the clinical observation of RNA rebound at the first time point available after treatment withdrawal. In contrast, pretreatment and posttreatment sequences from patients P01, P31 and P48 do not cluster and they were, therefore, considered re-infections. Although patients P01 and P31 became HCV RNA-positive again within 6 months after the end of treatment, the first sample taken at 4 weeks was negative, supporting our phylogenetic evidence of re-infection.

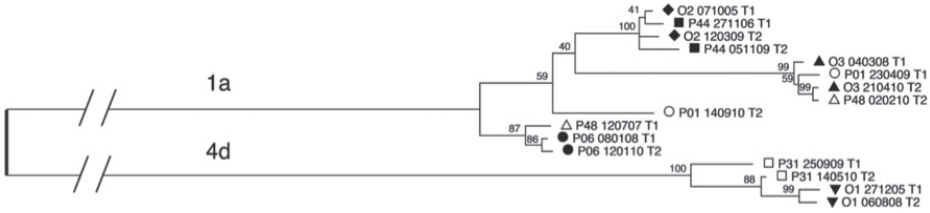

Figure 1. Phylogenetic tree of relapsers and patients with a re-infection with the same genotype. Phylogenetic tree of sequences before and after treatment from relapsers and patients with a re-infection with the same genotype. Relapsers are presented by filled symbols and re-infections are presented by open symbols. Each patient is presented by a unique symbol. The numbers in the labels indicate sampling dates. Note: re-infections with a different genotype are not presented in this tree.

The cumulative incidence of re-infection is demonstrated in Fig.2; after 2 years, the cumulative incidence of re-infection was 33% (95% CI 16–50).

In order to examine whether ALT levels are useful for indicating a new infection, we compared peak ALT levels during follow-up in patients with and without re-infection. The peak ALT levels were in general low (with a maximum of 160 U/l), although the median ALT peak during follow-up was higher in individuals with a re-infection than in those without a re-infection (P=0.01). Interestingly, in four cases with a re-infection, no increased ALT levels were observed, whereas in individuals without evidence of re-infection, ALT levels were elevated frequently (Fig. 3).

CD4 cell counts did not differ between patients with and without re-infection (Table 1). In addition, analysis of HIV load data from the eight of nine patients with a re-infection, who were on combination antiretroviral therapy (cART), showed that all patients had undetectable

HIV loads around the time of HCV re-infection. From one re-infected patient on cART, no HIV load data were available.

Analysis of the 21 MSM with behavioural data revealed that re-infected MSM (*n*=7) significantly more often reported noninjecting recreational drug use at inclusion than MSM without re-infection (*n*=14) (*P*=0.048). In this small study population, no statistically significant differences in sexual risk behaviour were found.

Of the 11 re-infected patients, four were treated for their re-infection; of those four, two achieved a sustained virologic response (SVR), one had a relapse, and one is still in follow-up for SVR time.

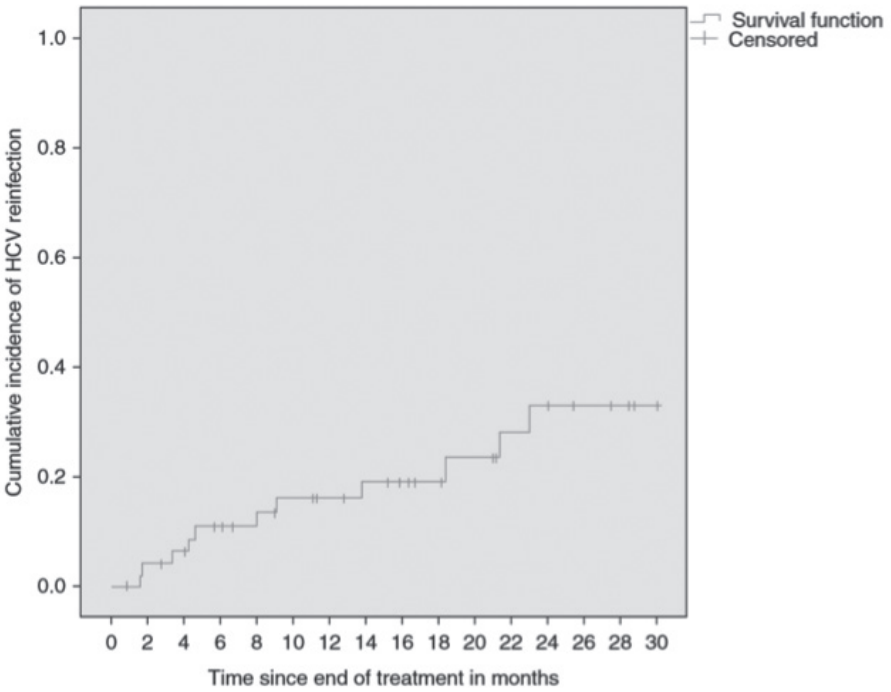

Figure 2. Cumulative incidence of hepatitis C virus (HCV) re-infection after successful treatment of primary HCV infection.

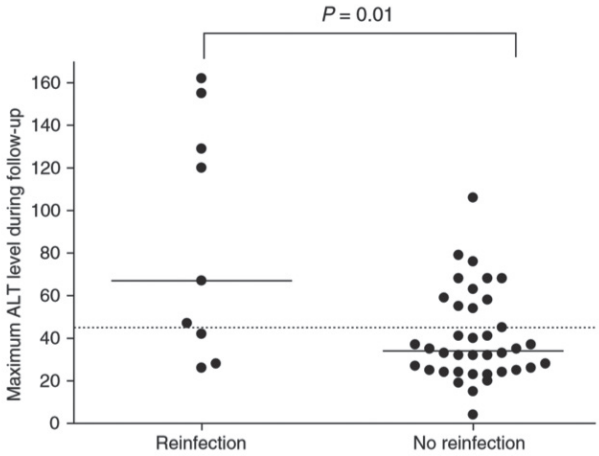

Figure 3. Peak alanine aminotransferase levels during follow up.
Peak alanine aminotransferase (ALT) levels in units per litre during the observation period (end of treatment until last negative or first positive timepoint).The dotted line represents the maximum normal ALT value.

Discussion

With this study, we demonstrate an alarmingly high incidence rate of sexually transmitted HCV re-infection among HIV-infected MSM previously successfully treated for primary HCV infection.

Most importantly, these findings stress the importance of repeated risk counselling for HCV transmission which should be provided not only before and during treatment but also after its completion. MSM re-infected with HCV showed higher rates of noninjecting recreational drug use. Sexual risk behaviour, including recreational drug use during sex, was highly prevalent (data not shown). Unfortunately, because of our relatively small study population with behavioural data, we were not able to examine risk behaviour more precisely and longitudinally.

The high incidence rate in this study implies that ALT levels, which can be elevated during an acute HCV infection, should be measured regularly in this population. Because these levels are not always elevated during acute infection or might not coincide with the test moment, as shown in Fig. 3, subsequent HCV RNA testing, especially in cases of high-risk behaviour, should be performed regularly, as antibodies remain in general present after successful treatment.

Along with risk behaviour, the role of biological susceptibility to HCV re-infection, although still unclear, is an important consideration. Importantly, discussion is ongoing whether previous infection with HCV can generate partial protective immunity to re-infection or increase the chance of clearance of re-infection.
Several studies that compared incidence rates of primary infection and re-infection among IDUs have presented results that argue both for [8, 18, 19] and against [6, 7, 10] this phenomenon. Differences between these studies are probably due to variations in intervals of testing, age of the participants, frequency of ongoing drug use and adjustment for behaviour in the analyses. The higher incidence of re-infection in our study compared with the incidence of primary infection in Amsterdam [2, 20] and elsewhere [3] indicates that, as expected, there is no complete protection. Yet, the finding that most re-infections in this study occurred with a different genotype compared with the primary infection suggests that genotype-specific immunity may develop in some individuals.
Additionally, underlying a persons' ability to develop protective immunity, genetic profiles may play a role in susceptibility to HCV re-infection. The association of genetic variations near the interleukin-28B (IL28B) region with spontaneous HCV clearance and treatment-induced clearance has been well described for HCV-mono-infected patients [21-28]. Similar results have been found regarding HCV treatment response in persons co-infected with HIV, although in this population the association is less clear for those treated during the acute infection [29-34]. The effect of IL28B polymorphisms on HCV re-infection has not been described. In accord with the effects in primary infection, one would expect the responder genotype to be at least more likely to allow clearance of re-infection than the nonresponder geno-type. Whether initial partial protective immunity is also more established in individuals with a beneficial IL28B genotype remains undetermined.
Apart from HCV-specific immune responses, HIV co-infection may play an important role. The exact role of HIV co-infection in primary sexually transmitted HCV infection is not well known. CD4 cell depletion in the gut may diminish the immune response against HCV sexual transmission [35]. Nevertheless, CD4 cell counts did not differ between patients with and without re-infection, indicating that the level of immune suppression caused by HIV co-infection does not influence the risk of re-infection following successful HCV treatment.

The results of this study may lead to a change in the current definitions of HCV relapse and re-infection. When no further genotyping or sequencing is performed, a recurrent HCV viraemia within 6 months after a negative test at the end of the treatment is currently considered a relapse [36]. Our study demonstrates that early recurrence of HCV could well be a re-infection with another genotype or strain. This distinction has important clinical ramifications and should, therefore, be recognized by clinicians. The definition of relapse or re-infection, especially in population with a high incidence of infection, should, therefore,

always be based on virological characteristics and not on a specific interval between the end of treatment and recurrence of HCV RNA in the serum.
Finally, from a clinical and cost-effective perspective, the results of this study will encourage discussion about the validity of repetitive HCV treatment in patients with numerous subsequent re-infections owing to continued risk behaviour.

Apart from small numbers, this study has other limitations. We have not studied the possible existence of HCV-mixed infections during primary infection. Therefore, we cannot entirely exclude the possibility that re-infections were previously existing infections that became detectable after a dominant strain had been cleared [37]. However, the fact that the median interval from the first HCV RNA-negative test to the first HCV RNA-positive test after treatment was 8 months, with several negative results in between, strongly suggests that all re-infections were recently transmitted infections.
Furthermore, as this was not a prospective study, time between tests was not similar for all patients, and a re-infection followed by a quick, spontaneous clearance might have been missed. Nevertheless, as the median time between tests was 3 months, we do not expect this to have significantly influenced the incidence rate.

In conclusion, a high incidence rate of HCV re-infection among HIV-infected MSM in Amsterdam was demonstrated in this study, emphasizing the need for more extensive risk behaviour counselling and secondary prevention by regular and frequent HCV testing in this population. Future research should focus on the reasons for continuing high-risk sexual behaviour in order to improve targeted prevention. In addition, research should try to elucidate the virological and host factors associated with re-infection and its outcome in HIV-infected individuals.

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Chapter 3.3

Treatment of acute hepatitis C virus infection in HIV-infected MSM: the effect of treatment duration

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Abstract

We evaluated hepatitis C virus (HCV) treatment and the effect of treatment duration (24 versus 48 weeks) on treatment outcome among 50 HIV-infected men who have sex with men with acute HCV infection in Amsterdam. Overall sustained virological response (SVR) rate was 76%. Treatment duration was not significantly associated with SVR (adjusted odds ratio=2.32; 95% confidence interval 0.39–13.97), suggesting that 24-week treatment may be sufficient for acute HCV infection in HIV-coinfected patients.

The widespread epidemic of sexually transmitted hepatitis C virus (HCV) infection among HIV-infected MSM has led to an increased number of early diagnoses of HCV infection and accordingly acute HCV treatment [1]. Although treatment of acute HCV in HIV-coinfected can be quite as successful as treatment of chronic HCV mono-infection [2-7], discussion is ongoing as to the optimum treatment strategy and specifically treatment duration for this specific population [8]. Our objective was therefore to examine the HCV treatment outcome and the effect of treatment duration among HIV-infected MSM with acute HCV infection in two hospitals in Amsterdam.

We included HIV-infected MSM diagnosed with an acute HCV infection presumably transmitted by male-to-male sexual contact; less than 2 years between the last negative result (HCV antibody or RNA) and the first positive result; and less than 2 years between estimated time of infection (midpoint between last negative and first positive test) and start of treatment. In one hospital, treatment was started with the intention to treat 24 weeks, in the other with the intention to treat 48 weeks. In both hospitals, regimens consisted of weekly peginterferon (Peg-IFN)-alpha-2a (180 mg/week) or (Peg-IFN)-alpha-2b (1.5 mg/kg bodyweight/week) and weight-based ribavirin daily.

Data collection included clinical data and the HCV virological response at week 4 (rapid virological response: RVR), week 12 (early virological response: EVR), at the end of treatment and 24 weeks after treatment; the latter defining treatment outcome as a sustained virological response (SVR) when HCV-RNA was undetectable. Logistic regression analysis was performed to examine the associations between different variables, including treatment duration, and treatment outcome.

Of 84 patients treated between 2003 and 2009, 52 met the inclusion criteria for this study, of whom two spontaneously cleared the virus and were excluded from analyses. Of the remaining, 42% (21/50) started treatment with the intention to treat 24 weeks and 58% (29/50) with the intention to treat 48 weeks. Nevertheless, treatment duration was not always exactly as intended, with the shorter regimen ranging from 22 to 36 weeks [median 24 weeks, interquartile range (IQR) 23–25] and the longer regimen ranging from 47 to 58 weeks (median 48 weeks, IQR 48–50).

Table 1 presents the clinical and virological characteristics, and determinants of treatment outcome of the 50 MSM at start of treatment.

Of the 50 patients, 12% (6/50) were either nonresponders who stopped treatment around week 12 (n=3) or persons who stopped earlier because of side-effects (n=3). At the end

of treatment, 88% (44/50) of patients were HCV-RNA negative, of whom 38 subsequently showed SVR and six relapsed. Overall, 76% (38/50) [95% confidence interval (CI) 64–88] obtained SVR. Virological data at week 4 and/or week 12 of treatment were available for 70% (n=35) and 78% (n=39) of the patients, respectively. An RVR was present in 19 of 35 patients (54%), of whom 18 achieved SVR (positive predictive value 95%). An EVR was present in 34 of 39 patients (87%), of whom 29 achieved SVR (positive predictive value 85%). In those without RVR, the negative predictive value was 44% (7/16); for those without EVR, it was 100%. Of patients without RVR and treated for 24 weeks, 40% (2/5) had SVR; among those without RVR and treated for 48 weeks, SVR was 64% (7/11) (P = 0.377).
In univariate analysis, no significant effect of longer treatment duration on SVR was found [odds ratio (OR) 1.53; 95% CI 0.42–5.66]. After adjusting for genotype, time between estimated infection and starting treatment, and RVR (see Table 1), the effect increased but remained nonsignificant (OR adjusted 2.23; 95% CI 0.43–11.46). RVR was significantly associated with SVR in both univariate and multivariate analysis. Because of correlation, EVR was only studied in univariate analysis.

Finally, a sensitivity analysis showed that the effect of treatment duration on outcome did not change substantially when analysis was restricted to patients with less than 1 year (n=40) or less than 6 months (n=19) between negative and positive HCV test and between estimated infection and start of treatment.

The high SVR rate of 76% in this study confirms that treatment of HCV infection can be successful in HIV-infected patients when started in the acute phase and should encourage clinicians to treat this complicated patient group. Although the adjusted odds of attaining SVR was 2.2 times higher for 48 weeks of treatment compared with 24 weeks, this difference was not statistically significant. This suggests that 24 weeks of treatment might be sufficient. This result strengthens the evidence for recommendations in current treatment guidelines for acute HCV infection in HIV coinfected patients [8-10]. The shorter regimen would be of great advantage for patients, as both peginterferon and ribavirin can cause serious side-effects.
High (pretreatment) CD4 cell counts have been found to be associated with spontaneous clearance and SVR in genotype 1 HCV-infection [11, 12]. Like Vogel et al. [7], we could not confirm this association. However, the majority of our patients had relatively high CD4 cell counts, making it difficult to demonstrate a potential effect of immunodeficiency. Our study also found no influence of concurrent cART, which suggests that coinfected patients with sufficient CD4 cell counts do not necessarily need to start cART before starting HCV treatment. Like others, we found that RVR and EVR are the strongest predictors for SVR [5, 7].

Even though our sample size is limited, our study is one of the largest to be undertaken by one group and results are comparable with that of the larger European multicentre cohort study [7]. Larger prospective studies are still of interest to specify new determinants for treatment decision guidance, such as the IL28b polymorphism [13-15].

In conclusion, the results of this retrospective cohort of HIV-infected MSM with acute HCV infection demonstrate that acute HCV treatment in this coinfected population can be very effective and 24 weeks treatment may be sufficient. The week 4 and 12 virological responses were strong predictors for good outcome and its role in clinical decisionmaking should be studied more extensively besides other predictors.

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Table 1. Characteristics of HIV-infected MSM with acute HCV infection treated in two hospitals in Amsterdam, from 2003 through 2009, and determinants of treatment outcome.

	All patients	SVR	Univariate analysis			Multivariate analysis		
	100% (50/50)	76% (38/50)	OR	95% CI	p-value	OR adjusted	95% CI	p-value
Treatment duration								
24 Weeks intended	42% (21/50)	71% (15/21)	1			1		
48 Weeks intended	58% (29/50)	79% (23/29)	1.53	0.42–5.66	0.521	2.23	0.43-11.46	0.336
Age (at estimated HCV infection)								
Median in years (IQR)	42 (36–47)	41 (35–47)	0.96	0.88–1.04	0.277			
Genotype					0.683			0.430
1	68% (34/50)	74% (25/34)	1			1		
2 or 3	6% (3/50)	67% (2/3)	0.72	0.06–8.94	0.798	0.58	0.03-10.39	0.708
4	26% (13/50)	85% (11/13)	1.98	0.37–0.71	0.428	2.95	0.45-19.32	0.259
Time from last negative HCV test to first positive HCV test								
Median in weeks (IQR)	18 (8–24)	18 (9–34)	0.99	0.96–1.02	0.407			
Time from HIV diagnosis to estimated HCV infection					0.488			
Median in years (IQR)	5 (2–9)	5 (1–10)						
<3 years	33% (16/48)	75% (12/16)	1					
3–6 years	25% (12/48)	67% (8/12)	0.67	0.13–3.47	0.630			
>6 years	42% (20/48)	85% (17/20)	1.89	0.36–0.03	0.455			

Table 1. Continued.

	All patients	SVR	Univariate analysis			Multivariate analysis		
	100% (50/50)	76% (38/50)	OR	95% CI	p-value	OR adjusted	95% CI	p-value
Time from estimated HCV infection to HCV treatment								
Median in weeks (IQR)	34 (19–51)	33 (18–51)						
<24 weeks	34% (17/50)	76% (13/17)	1			1		
≥24 weeks	66% (33/50)	76% (25/33)	0.96	0.24–3.80	0.955	0.59	0.09-3.74	0.577
Time from first HCV positive test to HCV treatment								
Median in weeks (IQR)	21 (11–34)	21 (11–33)	1.01	0.98–1.04	0.738			
ALAT-level during acute infection in U/l								
70–175	14% (7/49)	86% (6/7)	1					
≥175	86% (42/49)	76% (32/42)	0.53	0.06–4.97	0.581			
Median in 10^3 IU/ml (IQR)	715 (32–2560)	617 (10–2978)						
<150	31% (15/48)	94% (14/15)	1					
≥150	69% (33/48)	67% (22/33)	0.14	0.02–1.23	0.077			
CD4 cell count pretreatment					0.731			
Median in 10^6 copies/l (IQR)	450 (323–685)	440 (325–695)						
<380	31% (15/48)	80% (12/15)	1.67	0.32–8.59	0.541			
380–550	33% (16/48)	81% (13/16)	1.81	0.35–9.24	0.478			
>550	35% (17/48)	71% (12/17)	1					

Table 1. Continued.

	All patients	SVR	Univariate analysis			Multivariate analysis		
	100% (50/50)	76% (38/50)	OR	95% CI	p-value	OR adjusted	95% CI	p-value
cART-use during HCV treatment								
No	34% (17/50)	76% (13/17)	1					
Yes	66% (33/50)	76% (25/33)	0.96	0.24–3.80	0.955			
Rapid virological response (RVR)					0.066			0.043
No	32% (16/50)	56% (9/16)	1					
Yes	38% (19/50)	95% (18/19)	14.00	1.49–131.89	0.021	27.12	2.05-359.51	0.012
Not known	30% (15/50)	73% (11/15)	2.14	0.47–9.70	0.324	2.45	0.44-13.62	0.307
Early virological response (EVR)					0.027			
No	10% (5/50)	0% (0/5)	1					
Yes	68% (34/50)	85% (29/34)	59.00	5.47–8181.73	< 0.01			
Not known	22% (11/50)	82% (9/11)	41.80	3.11–6261.74	< 0.01			

CI, confidence interval; EVR, early virological response, HCV-RNA undetectable at week 12 of treatment; HCV, hepatitis C virus; MSM, men who have sex with men; OR, odds ratio; RVE, rapid virological response, HCV-RNA undetectable at week 4 of treatment; IQR, inter quartile range; SVR, sustained virological response, HCV-RNA undetectable at 24 weeks post-treatment

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Chapter 4

HCV risk behaviour, awareness and knowledge among HIV-infected MSM

Chapter 4.1

Risk factors for sexual transmission of hepatitis C virus among human immunodeficiency virus-infected men who have sex with men: a case-control study

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Abstract

Background

Since 2000, incidence of sexually acquired hepatitis C virus (HCV)-infection has increased among human immunodeficiency virus (HIV)-infected men who have sex with men (MSM). To date, few case-control and cohort studies evaluating HCV transmission risk factors were conducted in this population, and most of these studies were initially designed to study HIV-related risk behavior and characteristics.

Methods

From 2009 onwards, HIV-infected MSM with acute HCV infection and controls (HIV-monoinfected MSM) were prospectively included in the MOSAIC (MSM Observational Study of Acute Infection with hepatitis C) study at 5 large HIV outpatient clinics in the Netherlands. Written questionnaires were administered, covering sociodemographics, bloodborne risk factors for HCV infection, sexual behavior, and drug use. Clinical data were acquired through linkage with databases from the Dutch HIV Monitoring Foundation. For this study, determinants of HCV acquisition collected at the inclusion visit were analyzed using logistic regression.

Results

Two hundred thirteen HIV-infected MSM (82 MSM with acute HCV infection and 131 MSM without) were included with a median age of 45.7 years (interquartile range [IQR], 41.0–52.2). Receptive unprotected anal intercourse (adjusted odds ratio [aOR], 5.01; 95% confidence interval [CI], 1.63-15.4), sharing sex toys (aOR, 3.62; 95% CI, 1.04-12.5), unprotected fisting (aOR, 2.57; 95% CI, 1.02-6.44), injecting drugs (aOR, 15.62; 95% CI, 1.27-192.6), sharing straws when snorting drugs (aOR, 3.40; 95% CI, 1.39-8.32), lower CD4 cell count (aOR, 1.75 per cubic root; 95% CI, 1.19-2.58), and recent diagnosis of ulcerative sexually transmitted infection (aOR, 4.82; 95% CI, 1.60-14.53) had significant effects on HCV acquisition.

Conclusions

In this study, both sexual behavior and biological factors appear to independently increase the risk of HCV acquisition among HIV-infected MSM.

Introduction

Since 2000, outbreaks of sexually transmitted hepatitis C virus (HCV) have increasingly been reported among human immunodeficiency virus (HIV)-infected men who have sex with men (MSM) in Europe, Australia, Asia, and the United States [1-4]. Although some cases have been described to have acquired HCV through sexual route in the absence of HIV [5], the HIV-uninfected MSM population remains largely unaffected by this epidemic [4, 6-9]. After the increase of HCV incidence among HIV-infected MSM, 3 case-control studies have been conducted to elucidate determinants for HCV infection [10-12]. However, the 2 studies that included participants prospectively [11, 12] comprised small numbers of cases with acute HCV infection: 34 and 22, respectively. Independent risk factors that were identified in the 3 case-control studies were as follows: receptive unprotected anal intercourse (UAI), sex while high on methamphetamines [12], rectal bleeding, frequent receptive fisting, snorting cocaine or amphetamines [11], and group sex participation [10, 11]. Determinants for acute HCV infection among HIV-infected MSM have also been investigated retrospectively, in large HIV cohort studies in the United States [13], Switzerland [14], the Netherlands [8], and Japan [15]. These cohort studies led to accurate estimates of HCV incidence. However, because the initial scope of these cohorts was to study HIV, data on HCV-specific risk factors were limited. Independent risk factors for HCV acquisition that were identified in these studies were as follows: younger age [8], positive hepatitis B surface antigen test, alcohol abuse, lower CD4 cell count [13], illicit drug use, being on social benefits [15], injecting drug use (IDU) [13, 15], receptive UAI with multiple partners, and recent syphilis infection [13, 14]. Various other studies that addressed potential risk factors for HCV infection were limited by their study design (cross-sectional studies including prevalent infections and case reports) [5, 7, 16-21]. Because the majority of the studied MSM had an unknown duration of HCV infection, the reported risk behavior and clinical parameters at the time of study may differ significantly from those at the time of HCV acquisition. The MOSAIC (MSM Observational Study of Acute Infection with hepatitis C) cohort has been initiated to specifically study acute HCV infection among HIV-infected MSM. This cohort is one of the largest case-control studies conducted until now and therefore provides a unique opportunity to study biological and behavioral risk factors for sexual transmission of HCV.

Methods

Study population

The MOSAIC cohort is an open, ongoing, prospective, observational cohort, initiated to study determinants and sequelae of acute HCV infection among HIV-infected MSM [22].

The MOSAIC is a collaboration between the Public Health Service of Amsterdam, 5 large HIV outpatient clinics in the Netherlands (3 in Amsterdam, 1 in Rotterdam, and 1 in Utrecht), and the Dutch HIV Monitoring Foundation. Study subjects were HIV-infected MSM ≥18 years of age who (recently) had acquired an acute HCV infection. Acute HCV infection was defined as having an interval ≤6 months between the first positive HCV RNA test and the preceding negative HCV RNA or antibody test. To serve as controls, we aimed to include 2 HIV-infected MSM with no history of HCV, at the same hospital and in the period shortly after a case was identified. Inclusion started in 2009, and for the current study, we included all prospectively identified cases and controls who entered the study before February 2014.

Data collection

Hepatitis C virus antibody testing was performed using either AxSYM HCV 3.0 (Abbott Laboratories, Abbott Park, IL), ARCHITECT Anti-HCV (Abbott Laboratories), or Liaison XL (DiaSorin, Saluggia, Italy). Hepatitis C virus RNA tests were performed using either the VERSANT HCV RNA Qualitative Assay (Siemens Medical Solutions Diagnostics, Tarrytown, NY), COBAS Ampliprep/COBAS TaqMan (CAP/CTM; Roche Diagnostics, Mannheim, Germany), or the Abbott m2000 sp/rt system (Abbott Laboratories). Participants were followed up every 6 months, and more often during treatment of HCV infection, at their HIV outpatient clinic. At inclusion and follow-up visits, participants completed a self-administered questionnaire regarding sociodemographics, bloodborne risk factors classically related to HCV (eg, blood transfusion, IDU), sexual behavior with steady and/or casual sex partner(s), sex-related variables (eg, number of casual sex partners, meeting location), drug use before/during sex, and quality of life. Clinical data, such as date of HIV diagnosis, CD4 cell count, HIV viral load, and use of combination antiretroviral therapy (cART), were acquired for each visit through linkage with databases from the Dutch HIV Monitoring Foundation. The HCV-negative status of controls was assured by confirming the absence of HCV antibodies at inclusion and follow-up visits. The study protocol was approved by the local ethics committee, and all participants provided written informed consent to participate in the study.

Statistical analysis

Determinants of HCV infection that were collected using the baseline questionnaire administered at the inclusion visit were analyzed using logistic regression. In univariable analysis, Firth's penalized likelihood method [23] was used to obtain odds ratios (ORs) and 95% confidence intervals (CIs) when a cell in the analyzed table had zero frequency. Having unprotected sex only with a steady sex partner with a confirmed negative HCV status was not considered to be risk behavior for HCV. It has been suggested that HCV may also be transmitted from one receptive partner to another through (1) sharing contaminated sex toys or (2) contaminated gloves during fisting [11]. Fisting without gloves and fisting

with gloves in the presence of group sex are therefore defined as "unprotected fisting" throughout this study. We assumed that use of sex toys without sharing, and fisting with gloves in the absence of group sex, did not elevate the risk of HCV acquisition. The number of casual sex partners was transformed as ^{2}Log(N + 1); HIV viral load was modeled as ^{10}Log-increment above 50 copies/mL (values ≤50 were set at zero); CD4 cell count was cubic root transformed, to make the relationship with the outcome (HCV acquisition) more linear. To limit the number of risk factors included in multivariable logistic regression, we performed 2 separate analyses. The first analysis only included variables that [1] were expected to have a direct effect on HCV acquisition, ie, traditional risk factors and sexual behavior (see table 2B and 2C), and [2] were significantly associated with acute HCV infection in univariable analysis (P <.05). The second multivariable analysis included variables that were significantly associated in the first multivariable analysis (P <.05), variables related to sexual behavior that were strongly associated (P <.001) with acute HCV in univariable analysis, and variables that might facilitate or enhance HCV transmission (ie, recent ulcerative sexually transmitted infection [STI], lower CD4 cell count). When investigating the influence of these facilitating circumstances, we checked for the presence of interactions. We assumed that each facilitating factor had an equal interaction effect on all variables related to sexual risk behavior. When significant (P <.05), the interaction term was added to the final model; otherwise, the facilitating factor was included in the model without an interaction term. All analyses were performed using Stata Intercooled 13.1 (StataCorp, College Station, TX).

Results

General population characteristics

By February 1, 2014, 82 HIV-infected MSM with acute HCV infection (cases) and 131 HIV-infected controls had entered the MOSAIC study and completed the inclusion questionnaire. Characteristics of acute HCV infection (eg, HCV subtype, HCV RNA load at first positive visit, reported symptoms of acute infection) are shown in table 1. The vast majority of participants were included in the Amsterdam region (95.3%), and most were of Western European ethnicity (79.3%). The median age at study entry was 45.7 years, which was lower among cases (43.1 years) than controls (49.4 years; P < .001) (table 2A).

Risk factors for hepatitis C virus: univariable analysis

Apart from IDU, which was reported by 10 of 82 cases (12.2%) versus 2 of 131 controls (1.5%), none of the traditional bloodborne risk factors were associated with acute HCV in univariable analysis (table 2B). Sharing of needles was relatively uncommon among MSM who reported IDU (2 of 12; 16.7%). Sexual risk behavior was higher among MSM with acute

HCV compared with HCV-negative controls, and nearly all variables related to sexual risk behavior were associated with acute HCV infection. The following variables were strongly associated (P < .001) with acute HCV infection using univariable regression: receptive UAI, sharing sex toys, unprotected fisting, group sex participation, rimming, fingering, increasing number of casual sex partners, anal rinsing, rectal bleeding during or after having sex, and meeting casual sex partner(s) at sex parties (table 2C and D). Among 82 cases, 69 (84.1%) reported non-IDU in the 6 months preceding study entry versus 52.7% of the controls (69 of 131; OR, 2.60; 95% CI, 1.44–4.70; P =.002). Use of anally administered drugs was less common (reported by 18.3% of cases) than use of either orally administered drugs (OADs) or nasally administered drugs ([NADs] reported by 78.0% and 74.4% of cases, respectively). Oral administration of methamphetamines, ecstasy/3,4-methylenedioxymethamphetamine (MDMA), γ-hydroxybutyric acid (GHB)/γ-butyrolactone (GBL), and cannabis was associated with acute HCV infection. Nasal administration of amphetamines, cocaine, ketamine, and poppers was associated with HCV acquisition (all P < .001). When analyzed by means of administration, use of orally, anally, and nasally administered drugs were more frequently reported by cases than controls; ORs increased from 1.59 for the use of OADs only to 42.9 for injecting drugs (table 2E). Sharing straws was reported by 51% of MSM who reported consumption of NADs, and it was significantly associated with HCV acquisition (OR for snorting drugs with vs without sharing straws: 2.48; 95% CI, 1.14–5.37). Clinical variables associated with acute HCV were as follows: (1) lower CD4 cell count and higher HIV viral load at the last visit before inclusion (ie, for cases before acute HCV infection) and (2) shorter duration since HIV diagnosis (table 2F). These associations remained statistically significant in a sensitivity analysis only including those on cART at the study entry visit (N = 179; data not shown). In addition, the association between HCV acquisition and CD4 cell count remained significant in a sensitivity analysis that included only cases with a known HCV RNA negative test date preceding study entry (N = 52; OR, 1.49 per cubic root lower; 95% CI, 1.08–2.05; P =.015). Syphilis, chlamydia, and rectal gonorrhea infection in the previous 6 months were strongly associated with acute HCV infection (all P < .001). Both nonulcerative and ulcerative STIs were more often reported by MSM with acute HCV than MSM with no history of HCV (table 2F).

Risk factors for hepatitis C virus acquisition: multivariable analysis

In the first multivariable analysis that included variables that may directly cause transmission of acute HCV, receptive UAI (adjusted OR [aOR], 4.92; 95% CI, 2.00–12.10; P = .001), sharing sex toys (aOR, 6.08; 95% CI, 1.96–18.87; P = .002), unprotected fisting (aOR, 2.60; 95% CI, 1.11–6.10; P = .028), IDU (aOR, 11.26; 95% CI, 1.21–105.2; P = .034), and sharing straws when snorting drugs (aOR, 3.79; 95% CI, 1.71–8.42; P = .001) had significant effects on HCV acquisition. Group sex participation, rimming, and fingering had no significant effects on HCV

acquisition (Figure 1A); these variables were therefore omitted in the second multivariable analysis. In the second multivariable analysis that included a broader range of variables, none of the studied interactions were significant, and they were therefore omitted in the presented model. In this model, receptive UAI (aOR, 5.01; 95% CI, 1.63–15.43; P = .005), sharing sex toys (aOR, 3.62; 95% CI, 1.04–12.52; P = .042), unprotected fisting (aOR, 2.57; 95% CI, 1.02–6.44; P = .044), IDU (aOR, 15.62; 95% CI, 1.27–192.6; P = .032), sharing straws when snorting drugs (aOR, 3.40; 95% CI, 1.39–8.32; P = .007), lower CD4 cell count (aOR, 1.75 per cubic root lower; 95% CI, 1.19–2.58; P = .004), and recent ulcerative STI (aOR, 4.82; 95% CI, 1.60– 14.53; P = .005) had significant effects on HCV acquisition. The number of casual sex partners had no significant effect on HCV acquisition; nor did anal rinsing, rectal bleeding, and sex parties as meeting location for casual sex partners (Figure 1B). In an exploratory post hoc analysis, we calculated a risk score for each MSM, ranging from 0 to 6, depending on the number of the following sexual behavior acts in the 6 months preceding study entry: receptive UAI, sharing toys, unprotected fisting, group sex participation, rimming, fingering. In multivariable analysis, men with a risk score of 4 had an aOR of 8.63 (95% CI, 1.49–50.0), those with risk score of 5 had an aOR of 10.3 (95% CI, 1.54–68.4), and 12 men with a risk score of 6 were excluded from the analysis because all 12 were cases, leading to a zero cell count. Men with risk scores of 1, 2, and 3 of these sex acts had aORs of 2.61 (95% CI, .52–13.1), 2.16 (95% CI, .38– 12.4), and 2.40 (95% CI, .48–12.0), respectively, compared with MSM with a zero risk score. In this analysis, the aOR for the variables that were added in the second multivariable analysis were comparable (data not shown).

Table 1. Characteristics of acute HCV infection among 82 HIV-infected men who have sex with men[a]

Characteristic	Value
Year of HCV diagnosis	2010.5 (2010-2011)
No. of days between last negative and first positive HCV RNA sample[b]	148 (116-186)
No. of days between last negative and first positive anti-HCV sample	164 (118-218)
HCV load of first positive HCV RNA sample	$4.5E10^5$ ($1.2\ E10^4$ - $3.3\ E10^6$)[c]
Change in ALT concentration between last negative and first positive HCV sample[d]	99 (19–422)[e]
Peak ALT between last negative HCV sample and ≤3 months after the first positive HCV sample	350 (164-653)[e]
HCV subtype; n (%)	
1a	52 (63.4)
1b	6 (7.3)
2b	10 (12.2)
4d	11 (13.4)
Unknown/not typable	3 (3.7)
Reported symptoms of acute infection; n (%)	
Joint pain	7 (8.5)
Jaundice	3 (3.7)
Fatigue	38 (46.3)
Muscle pain	14 (17.1)
Flu-like symptoms	23 (28.1)
Loss of appetite	17 (20.7)

Abbreviations: ALT, alanine aminotransferase; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MOSAIC, MSM Observational Study of Acute Infection with hepatitis C. [a]MOSAIC study, the Netherlands, 2009-2014. Numbers are median (interquartile range) unless indicated otherwise. [b]Data available for 52 of 82 cases. [c]IU/mL. [d]Data available for 58 of 82 cases. [e]U/L.

Table 2. Determinants of acute HCV infection among 213 men who have sex with men, of whom 82 acquired acute hepatitis C infection.

Characteristic	Subcategory	82 HIV+ MSM with acute HCV N (%)	131 HIV+ MSM without HCV N (%)	Odds Ratio (95% CI)	*P* value
2A: SOCIO-DEMOGRAPHIC CHARACTERISTICS					
Age (median, IQR)		43.1 (39.2-47.6)	49.4 (42.3-54.8)	.94 (.38-.72) per 10y increment	<.001
Ethnicity	West-European	65 (79.3)	104 (79.4)	1	.742
	Other	15 (20.7)	27 (20.6)	1.13 (.56-2.27)	
Living situation	Alone	32 (39.0)	57 (43.5)	1	.755
	With steady sex partner	38 (46.3)	54 (41.2)	1.25 (.69-2.28)	
	Other	12 (14.6)	20 (15.3)	1.07 (.46-2.47)	
Educational level	Middle & low	27 (32.9)	35 (26.7)	1	.277
	High	53 (64.6)	96 (73.3)	.72 (.39-1.31)	
2B: TRADITIONAL RISK FACTORS FOR HCV [12M]					
Injecting drug use (IDU)		10 (12.2)	2 (1.5)	8.96 (1.91-42.01)	.005
Tattoo		6 (7.3)	9 (6.9)	1.07 (.37-3.12)	.901
Blood transfusion		0 (0.0)	2 (1.5)	.31 (.01-6.62)	.456
Surgery		7 (8.5)	15 (11.5)	.72 (.28-1.85)	.498
Endoscopy		9 (11.0)	15 (11.5)	.95 (.40-2.29)	.915

Table 2. Continued.

Characteristic	Subcategory	82 HIV+ MSM with acute HCV N (%)	131 HIV+ MSM without HCV N (%)	Odds Ratio (95% CI)	*P* value
2C: SEXUAL BEHAVIOR [6M]					
Insertive/receptive unprotected anal intercourse (iUAI/rUAI)	No UAI / only with HCV-negative steady sex partner	10 (12.2)	61 (46.6)	1	<.001
	Only iUAI with HCV-positive/ unknown sex partner(s)	3 (3.7)	15 (11.5)	1.22 (.30-4.99)	
	(Also) rUAI with HCV-positive/ unknown sex partner(s)	69 (84.1)	55 (42.0)	7.65 (3.59-16.31)	
Sharing of sex toys	No toys used / only shared toys with HCV-negative steady sex partner	55 (67.1)	126 (96.2)	1	<.001
	Toys shared	27 (32.9)	5 (3.8)	12.37 (4.53-33.81)	
Unprotected fisting	No fisting / gloves used and no group sex reported	42 (51.2)	113 (86.3)	1	<.001
	No gloves used / gloves used and group sex reported	40 (48.8)	18 (13.7)	5.98 (3.09-11.56)	
Group sex participation	No group sex	29 (35.4)	84 (64.1)	1	<.001
	2 sex partners (i.e., only threesomes)	9 (11.0)	15 (11.5)	1.74 (.69-4.40)	

Table 2. Continued.

Characteristic	Subcategory	82 HIV+ MSM with acute HCV N (%)	131 HIV+ MSM without HCV N (%)	Odds Ratio (95% CI)	*P* value
	≥3 sex partners	44 (53.7)	29 (22.1)	4.39 (2.34-8.26)	
Rimming	No rimming / only with HCV-negative steady sex partner	29 (35.4)	80 (61.1)	1	<.001
	(Also) with HCV-positive/ unknown sex partner(s)	53 (64.6)	51 (38.9)	2.87 (1.62-5.08)	
Fingering	No fingering / only with HCV-negative steady sex partner	28 (34.1)	75 (57.3)	1	.001
	(Also) with HCV-positive/ unknown sex partner(s)	54 (65.9)	56 (42.7)	2.58 (1.46-4.58)	
2D: SEX-RELATED VARIABLES [6M]					
Having a steady sex partner		48 (58.5)	79 (60.3)	.93 (.53-1.63)	.798
Age of steady sex partner (median, IQR)		43 (40-49)	45 (36-50)	1.05 (.67-1.63) per 10y increment	.831
Number of casual sex partners Continuous		11 (5-23)	5 (0-10)	1.38 (1.18-1.62) per doubling	<.001
Categorical					
	0	8 (9.8)	36 (27.5)	1	<.001
	1-9	25 (30.5)	47 (35.9)	2.39 (.97-5.93)	
	10-19	19 (23.2)	29 (22.1)	2.95 (1.13-7.70)	

Table 2. Continued.

Characteristic	Subcategory	82 HIV+ MSM with acute HCV N (%)	131 HIV+ MSM without HCV N (%)	Odds Ratio (95% CI)	*P* value
	20-49	22 (26.8)	13 (9.9)	7.62 (2.72-21.29)	
	≥50	8 (9.8)	6 (4.6)	6.00 (1.62-22.16)	
Anal rinsing	No anal rinsing / only with HCV-negative steady sex partner	18 (22.0)	72 (55.0)	1	<.001
	Anal rinsing with HCV-positive/unknown sex partner(s)	64 (78.0)	59 (45.0)	4.34 (2.32-8.11)	
Rectal bleeding during and/or after sex	No bleeding / only after sex with HCV-negative steady sex partner	46 (56.1)	117 (89.3)	1	<.001
	Bleeding after sex with HCV-positive/unknown sex partner(s)	36 (43.9)	14 (10.7)	6.54 (3.23-13.24)	
Piercing(s) in genital region	No piercing(s)	73 (89.0)	125 (95.4)	1	.218
	Yes, self	3 (3.7)	2 (1.5)	2.57 (.42-15.73)	
	Yes, steady sex partner	6 (7.3)	4 (3.1)	2.57 (.70-9.40)	
Received money for sex		4 (4.9)	5 (3.8)	1.29 (.34-4.96)	.709
Meeting location of casual sex partner(s)					
Leather bar / leather party		20 (24.4)	21 (16.0)	1.69 (.85-3.36)	.134
Gay bar		22 (26.8)	27 (20.6)	1.41 (.74-2.70)	.295

Table 2. Continued.

Characteristic	Subcategory	82 HIV+ MSM with acute HCV N (%)	131 HIV+ MSM without HCV N (%)	Odds Ratio (95% CI)	*P* value
Internet		51 (62.2)	55 (42.0)	2.27 (1.29-4.00)	.004
Public cruising area		5 (6.1)	16 (12.2)	.47 (.16-1.33)	.153
Sex party		28 (34.2)	10 (7.6)	6.27 (2.85-13.83)	<.001
Gay sauna		20 (24.4)	34 (26.0)	.92 (.49-1.74)	.799
Darkroom		21 (25.6)	32 (24.4)	1.07 (.56-2.01)	.846
Abroad		12 (14.6)	20 (15.3)	.95 (.44-2.07)	.900
Other		8 (9.8)	10 (7.6)	1.31 (.49-3.46)	.589
2E: DRUG USE BEFORE / DURING SEX [6M]					
Orally administered drugs (OADs)					
No OADs used		18 (22.0)	81 (61.8)	.18 (.09-.33)	<.001
2C-B		0 (0.0)	1 (0.8)	.52 (.02-13.10)	.696
Amphetamines		6 (7.3)	4 (3.1)	2.51 (.69-9.17)	.165
Cannabis		31 (37.8)	27 (20.6)	2.34 (1.27-4.33)	.007
Cocaine		4 (4.9)	2 (1.5)	3.31 (.59-18.48)	.173
Ecstacy / MDMA		57 (69.5)	32 (24.4)	7.05 (3.81-13.06)	<.001
GHB / GBL		39 (47.6)	22 (16.8)	4.49 (2.39-8.44)	<.001
Ketamines		1 (1.2)	0 (0.0)	4.84 (.19-12.2)	.336
Methamphetamines		9 (11.0)	0 (0.0)	33.99 (1.95-592.5)	.016

Table 2. Continued.

Characteristic	Subcategory	82 HIV+ MSM with acute HCV N (%)	131 HIV+ MSM without HCV N (%)	Odds Ratio (95% CI)	*P* value
Poppers		4 (4.9)	3 (2.3)	2.19 (.48-10.04)	.314
Anally administered drugs (AADs)					
No AADs used		67 (81.7)	129 (98.5)	.07 (.02-.31)	.001
Amphetamines		4 (4.9)	2 (1.5)	3.31 (.59-18.48)	.173
Cannabis		1 (1.2)	0 (0.0)	4.84 (.19-12.2)	.336
Cocaine		8 (9.8)	1 (0.8)	14.05 (1.72-114.6)	.014
GHB / GBL		1 (1.2)	1 (0.8)	1.60 (.10-26.02)	.739
Ketamines		7 (8.5)	2 (1.5)	6.02 (1.22-29.73)	.028
Methamphetamines		3 (3.7)	1 (0.8)	4.94 (.50-48.28)	.170
Poppers		1 (1.2)	0 (0.0)	4.84 (.19-12.2)	.336
Nasally administered drugs (NADs)					
No NADs used		21 (25.6)	83 (63.4)	.20 (.11-.37)	<.001
Amphetamines		23 (28.0)	4 (3.1)	12.38 (4.10-37.40)	<.001
Cocaine		38 (46.3)	19 (14.5)	5.09 (2.65-9.77)	<.001
Ketamines		30 (36.6)	9 (6.9)	7.82 (3.47-17.62)	<.001
Methamphetamines		4 (4.9)	0 (0.0)	15.08 (.80-283.8)	.070
Miau-miau		2 (2.4)	2 (1.5)	1.61 (.22-11.68)	.636
Poppers		50 (61.0)	42 (32.1)	3.31 (1.86-5.89)	<.001

Table 2. Continued.

Characteristic	Subcategory	82 HIV+ MSM with acute HCV N (%)	131 HIV+ MSM without HCV N (%)	Odds Ratio (95% CI)	*P* value
Methods of administering drug(s), combined	No drugs used	13 (15.9)	62 (47.3)	1	<.001
	Only OADs used	5 (6.1)	15 (11.5)	1.59 (.49-5.15)	
	NADs used, no straws shared	22 (26.8)	33 (25.2)	3.18 (1.42-7.11)	
	NADs used, straws shared	33 (40.2)	20 (15.3)	7.87 (3.48-17.80)	
	Injected drugs	9 (11.0)	1 (0.8)	42.92 (5.00-368.8)	
2F: CLINICAL CHARACTERISTICS					
CD4 cell count at the HCV-negative visit preceding study entry (cells/μL)		500 (400-670)	590 (450-760)	1.41 (1.08-1.85) per cubic root lower	.012
Nadir CD4 cell count until the HCV-negative visit preceding study entry (cells/μL)		260 (170-350)	210 (110-310)	.82 (.67-1.01) per cubic root lower	.057
No. of years between first HIV-positive test and study entry visit[a]		6.5 (3.2-9.7)	9.1 (4.0-15.4)	.92 (.88-.97)	.001
HIV load at HCV-negative visit preceding study entry (copies/mL)		<50 (<40-12525)[b]	<40 (<40-<50)[b]	1.59 (1.18-2.12) per ^{10}Log increment	.002
Use of cART at HCV-negative visit preceding study entry[a]		68/81 (84.0)	111/122 (91.0)	.52 (.22-1.22)	.133
STIs (self-reported) [6M]					
Syphilis		20 (24.4)	7 (5.3)	5.71 (2.29-14.24)	<.001

Table 2. Continued.

Characteristic	Subcategory	82 HIV+ MSM with acute HCV N (%)	131 HIV+ MSM without HCV N (%)	Odds Ratio (95% CI)	*P* value
Chlamydia trachomatis		29 (35.4)	13 (9.9)	4.97 (2.39-10.31)	<.001
Rectal gonorrhea		19 (23.2)	5 (3.8)	7.60 (2.71-21.30)	<.001
Herpes genitalis		1 (1.2)	1 (0.8)	1.60 (.10-26.02)	.739
Hepatitis B virus		0 (0.0)	1 (0.8)	.53 (.02-13.10)	.696
LGV		9 (11.0)	2 (1.5)	7.95 (1.67-37.80)	.009
Urethral gonorrhea		14 (17.1)	6 (4.6)	4.29 (1.58-11.67)	.004
Other (e.g., genital warts, oral gonorrhea)		2 (2.4)	3 (2.3)	1.07 (.17-6.52)	.944
STIs (combined)	No STIs	34 (41.5)	109 (83.2)	1	<.001
	≥1 non-ulcerative STI	22 (26.8)	13 (9.9)	5.43 (2.47-11.91)	
	≥1 ulcerative STI[c]	26 (31.7)	9 (6.9)	9.26 (3.96-21.67)	

Continuous variables are presented as median (interquartile range). Abbreviations: 2C-B, 2,5-dimethoxy-4-bromophenethylamine hydrochloride; 6M, up to 6 months preceding study entry; 12M, up to 12 months preceding study entry; cART, combination antiretroviral therapy; CI, confidence interval; GBL, γ-butyrolactone; GHB, γ-hydroxybutyric acid; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HIV+ MSM, HIV-infected men who have sex with men; LGV, lymphogranuloma venereum; STI, sexually transmitted infection. [a] Data missing for 1 case and 9 controls. [b] Fifty of 75 (66.7%) cases and 99 of 112 (88.4%) controls had undetectable HIV viral load. [c] Ulcerative STI: syphilis, herpes genitalis, LGV.

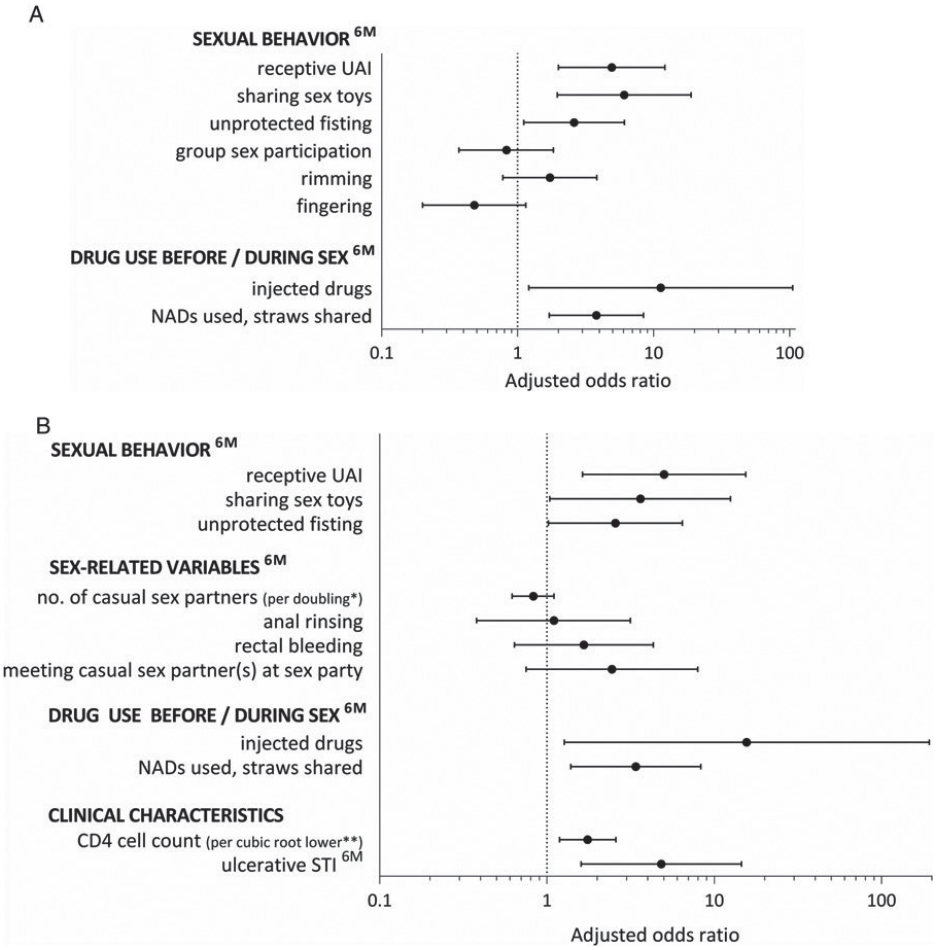

Figure 1. A, Cleveland dot plot showing results of a multivariable model including variables that potentially have direct effects on acquisition of acute hepatitis C virus (HCV); model 1 of 2. B, Cleveland dot plot showing (1) results of a multivariable model including variables that potentially have direct effects on acquisition of acute HCV and (2) variables that potentially facilitate transmission of acute HCV, model 2 of 2. *, modeled as ^{2}Log(N + 1); **, at the HCV-negative visit preceding study entry, cells/μL. ^{6M}, up to 6 months preceding study entry; NADs, nasally administered drugs; UAI, unprotected anal intercourse; ulcerative STI, any of the following sexually transmitted infections: syphilis, herpes genitalis, lymphogranuloma venereum. Data were collected among 213 human immunodeficiency virus (HIV)-infected men who have sex with men (MSM), 82 of whom had acute HCV infection. All participated in the MOSAIC (MSM Observational Study of Acute Infection with hepatitis C) study, the Netherlands, 2009–2014.

Discussion

We conducted a comprehensive study on risk factors for transmission of HCV among HIV-infected MSM showing that receptive UAI, sharing sex toys, unprotected fisting, IDU, sharing straws when snorting drugs, lower CD4 cell count, and recent ulcerative STI have independent effects on HCV acquisition among HIV-infected MSM. Most of these variables were not independently associated with acute HCV in previously conducted case-control studies [10-12], probably due to a lack of statistical power, or because these studies did not incorporate data on all topics mentioned. Other transmission routes that previously have been suggested (eg, rectal bleeding [11]) were measured, but they had no significant effect on HCV acquisition in our multivariable analysis. MSM with acute HCV infection were younger than controls, concurrent with other recent studies [8, 24, 25]. In addition, cases had shorter duration of (known) HIV infection, but they had lower CD4 cell counts preceding HCV acquisition than HCV-negative controls. Although the absolute difference in median CD4 cell count was 90 cells/μL (ie, 500 for cases vs 590 for controls), the effect remained significant in multivariable analysis (also when the CD4 cell count obtained from the penultimate visit was analyzed). An effect of lower CD4 cell count on HCV acquisition has been suggested before, but studies addressing this topic are scarce. Witt et al [13] reported significantly higher HCV incidence rates among HIV-infected MSM with lower CD4 cell counts (modeled per 100 cells/μL for those with a range of 0–500). In contrast, in the Swiss HIV Cohort Study [14] and the Amsterdam Cohort Study among MSM [8], effects of CD4 cell count on HCV acquisition were marginal and not significant. The lower CD4 cell count that we observed may be a consequence of STI other than HCV [26] and thereby an indirect marker for earlier increased sexual risk behavior. The significant effect of a reduced CD4 cell count may partly explain why sexual transmission of HCV infection seems to be rare among HIV-negative MSM [1, 5]. Alternatively, lower sexual risk behavior among HIV-negative MSM might explain the absence of both HIV and HCV in this group. Another reason there may be increased HCV infection among HIV-infected MSM compared with HIV-negative MSM could be due to serosorting (ie, establishing HIV concordance in advance to practicing UAI) [27]. The associations of HCV acquisition with group sex participation, the number of casual sex partners, and meeting location of casual sex partners lost significance when corrected for sexual behavior in multivariable analysis. Hence, the sexual behavior itself (eg, having receptive UAI or not) appeared to outweigh the number of casual sex partners (either simultaneous or consecutive) in contributing to risk of acute HCV infection. In addition, the risk score analysis also showed that men who participated in 4 or more different risky sex acts in the previous 6 months were much more likely to have acquired HCV than men with less than 4 sex acts. This finding emphasizes that there are differences in the degree of sexual risk taking among MSM, and it indicates that practicing multiple risky

sexual techniques may substantially increase the risk of HCV acquisition. The majority of HCV infections in our study was of genotype 1 and 4, in line with earlier reports [7, 8, 10, 12, 14, 28]. We report a relatively high proportion of subtype 2b infections (12.2%); this subtype is likely to have been introduced more recently in the MSM population in the Netherlands [8, 29]. In contrast to recent findings in the United Kingdom [30], we did not observe a high prevalence of so-called "chem-sex" or "slamming" (ie, injection of methamphetamines or mephedrone in combination with high-risk sexual practices). Injecting drug use and, more specifically, sharing needles was relatively uncommon in our study. Still, IDU remains a major risk factor for transmission of HCV. Sharing straws was reported by more than half of the participants that had recently consumed NADs; it had a significant effect on HCV acquisition in the multivariable analyses. Although sharing of contaminated straws could potentially increase HCV transmission [31], a systematic review regarding this topic concluded that current studies failed to show clear associations of non-IDU behavior with HCV infection [32]. Hence, whether or not sharing straws is a direct or indirect route of HCV transmission remains to be elucidated. Administration of NADs, or drug use in general, could be a marker for risky behavior that we did not measure, eg, longer sex episodes or having more rough sex. This may lead to dehydration of mucosal surfaces, which in turn may increase chances of permucosal transmission of HCV due to microtrauma or rectal bleeding [33]. A reason for not finding an association of HCV acquisition with rectal bleeding in our multivariable analysis might be underreporting, because not all bleeding is visible during or after sex [11]. This study has some limitations. The sample size still limits the number of parameters that could be estimated in multivariable analysis (including interaction terms). Diagnosis of recent STI was self-reported, and use (or sharing) of lubricant was not assessed; the latter might also facilitate HCV transmission. Various HIV-related characteristics were studied, but the precise duration of HIV infection could only be estimated for a minority of the population because for most participants, no data on HIV-negative test results were available. Because different risk behaviors might be correlated, it could be difficult to determine which is the more important one leading to HCV acquisition. However, correlation is unlikely to be a significant factor in our study, because it would have led to less significant effects of different sexual behaviors in multivariable analysis. As characteristics of local epidemics may differ (eg, the difference in the practice of chem-sex reported in this study compared with reports from the United Kingdom [30]), and the majority of participants in our study were from Amsterdam and the Netherlands, our results may not be widely generalizable to other areas.

Conclusions

This study showed significant effects of both biological and behavioral risk factors on HCV acquisition among MSM. In the ongoing HCV epidemic in which HIV-infected MSM with high-risk sexual behavior were probably infected first, MSM with lower risk profiles may become increasingly affected by acute HCV [7, 33]. Frequent testing of MSM at highest risk for (re-)infection may lead to earlier diagnosis and treatment initiation, which in turn could also limit ongoing transmission in the MSM population. In addition, tailored education and behavioral interventions are therefore needed to avoid ongoing transmission of HCV in the MSM population. Future longitudinal studies should preferably focus on temporal changes in risk behavior among HIV-infected MSM, to evaluate possible risk reduction strategies for HCV (re-)infection.

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Chapter 4.2

High awareness of hepatitis C virus (HCV) but limited knowledge of HCV complications among HIV-positive and HIV-negative men who have sex with men

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Abstract

Background

Hepatitis C virus (HCV) has emerged as a sexually transmitted infection among HIV-positive men who have sex with men (MSM) in high-income countries. Little is reported about HCV awareness among MSM, although this is essential for developing targeted prevention strategies. We, therefore, studied HCV awareness and knowledge among HIV-positive and HIV-negative MSM from the Amsterdam Cohort Studies (ACS).

Methods

During two visits, 1 year apart and starting in October 2007, MSM from the ACS answered questions regarding HCV awareness, knowledge of HCV transmission (7 items), complications (8 items) and sexual risk behaviour. We examined the percentage of HCV awareness and correctly answered knowledge items, and whether awareness and knowledge improved significantly over time. Using logistic regression, we studied whether HIV status and sexual risk behaviour were associated with awareness.

Results

Seventy percent (312/444) of HIV-negative and 80% (74/92) of HIV-positive MSM reported to have ever heard of HCV on the first visit. Overall, awareness increased with 9% between the first and second visit ($p < 0.001$). In multivariate analysis the association of group sex with HCV awareness was borderline significant (OR 1.49, 95% CI 0.97–2.30). Compared with knowledge of transmission routes, knowledge of complications appeared to be limited.

Conclusions

In the ACS, awareness of HCV is high, particularly among those reporting group sex, an important risk factor for HCV transmission. The majority of participants had good knowledge of transmission routes, but limited knowledge of complications of chronic HCV infection. HCV prevention messages could be strengthened, therefore, by further addressing the complications of HCV infection.

Introduction

Since the first report on sexually transmitted hepatitis C virus (HCV) infection in HIV-positive men who have sex with men (MSM) in 2004 [1], an increasing number of studies has been published regarding HCV molecular epidemiology, risk factors and HCV treatment in this population [2-15]. This epidemic started in the late nineties and has spread to several urban areas worldwide [16]. Both phylogenetic studies and quantitative studies with risk-behaviour questionnaires suggest that the transmission of HCV among MSM occurs primarily among HIV-positive MSM engaging in high-risk sexual behaviour, such as unprotected anal intercourse, sharing toys, fisting, group sex and recreational drug use before or during sex [17]. Although the role of HIV and the specific transmission routes remains unclear, the results of studies on risk factors for HCV transmission among MSM have led to the development of recommendations for HCV prevention.

To be effective, prevention messages should be tailored to the awareness, knowledge, attitudes and behaviour regarding a targeted disease in a population. There is a limited number of studies regarding awareness and knowledge of HCV among MSM. In a study among 90 HIV-positive MSM visiting an HIV-clinic in London in 2005, 69% reported to be aware of HCV [18]. In this study, men at high risk (>1 partner or reporting unprotected passive anal intercourse or fisting) were more likely to be aware of HCV than men at low risk. A recent study among 333 MSM in Belgium, including both HIV-negative and HIV-positive men, demonstrated that awareness of transmission routes of HCV was low and that information on prevention measures was needed [19].

In Amsterdam, where HCV has also spread in the MSM population, recommendations for HCV prevention have been communicated since 2007 through leaflets at the outpatient clinic for sexually transmitted infections (STI) at the Public Health Service, and since August 2009 through leaflets at gay venues and on a website for gay health information (2009). In addition, in November 2007 the Amsterdam STI clinic started routine HCV (antibody) testing of HIV-positive MSM and of MSM who did not know their HIV status.

In the present study, we wished to evaluate the awareness of HCV and knowledge of HCV transmission, treatment and complications among MSM participating in the Amsterdam Cohort Studies (ACS). We explored the percentage of HCV awareness and accurate knowledge and whether HIV status and risk behaviour were associated with awareness. Furthermore, considering the increase in attention to the HCV epidemic by way of prevention activities in the Netherlands, we examined whether percentage of awareness and knowledge increased over time and which determinants were associated with becoming aware of HCV.

Methods

Study population

The ACS among MSM is an open and ongoing prospective cohort study initiated in 1984 to investigate the epidemiological, behavioural and psychosocial aspects of HIV/AIDS and other STI among MSM [20, 21]. Participants visit the cohort every six months for HIV- and STI-screening, blood sample storage and filling out questionnaires on sexual risk behaviour and related psychosocial determinants. As part of other studies, HCV-antibody tests were performed retrospectively for all participants until 2003 [13] (only HCV-positive participants were informed of this screening and the results), and prospectively from October 2007 until 2010 for HIV-negative men and onwards for HIV-positive men.

Data collection

Starting in October 2007, all MSM visiting the cohort were asked to answer questions regarding HCV awareness and knowledge in addition to the standard questionnaire on sexual risk behaviour. All questions were paperbased and self-administered. If they reported that they were aware of HCV (answered "yes" to "Have you heard of the hepatitis C virus?"), they were subsequently asked to answer questions regarding knowledge of HCV treatment, transmission and complications. Approximately one year after fulfilment of this first questionnaire the same questions were repeated at a follow-up visit, to examine whether awareness and knowledge increased over time.

Statistical analyses

First, we calculated the percentage of HCV awareness in the first and second visit during which participants answered questions about HCV. In addition, we examined whether the percentage of awareness significantly increased between these visits among all participants with two visits, using the McNemar test for paired proportions. Second, in univariate and multivariate logistic regression analyses we examined whether HIV status, age, education and risk behaviour over the previous six months, were associated with awareness in the first visit (see Table 1 for definitions of determinants).

Third, we studied which variables as reported in the second visit were associated with becoming aware of HCV over time for all study participants not aware on the first visit (Table 2).

In all analyses, besides studying specific risk behaviour variables, risk behaviour was also dichotomized to high- and low-risk sexual behaviour, based on results of studies on risk factors for HCV [2, 13, 15]. High-risk sexual behaviour for HCV was defined as having had unprotected passive anal intercourse with a casual partner in the previous six months and/or having been fisted by a casual partner in the previous six months and/or having

participated in group sex (defined as having sex with more than 3 partners at one occasion) in the previous six months.

In addition, those persons reporting to be aware of HCV answered questions regarding HCV testing, treatment (awareness of treatment and ever treated) and knowledge items on transmission and complications (see Table 3 for the specific questions on knowledge items). We assessed the proportion of persons tested for HCV, awareness of treatment and the number of correct knowledge items on the first and second visit among those aware on both visits. We examined whether knowledge changed over time for all participants with two visits. Finally, differences in knowledge between those who were HIV positive and those HIV negative and between participants with high-risk behaviour and low-risk behaviour were examined at the first visit.

Characteristics were described and differences between groups were tested using the Chi-square, Fischer's exact test, McNemar test or Mann-Whitney-U-test. Univariate and multivariate analysis were carried out using logistic regression. All variables with a p-value ≤ 0.10 in univariate analysis were included in the multivariate model. An association was considered statistically significant with a p-value of ≤0.05. Changes in the proportion of awareness and knowledge over time were tested using the McNemar-test for awareness and individual knowledge items and the paired sample t-test for mean total score on knowledge. SPSS version 19.00 was used for all analyses.

Results

Characteristics study population

Between October 2007 and January 2009, 539 of 540 participants of the ACS answered the question about HCV awareness for the first time and were thus included in the study; 82% of participants (444/540) were HIV negative, 17% (92/540) were HIV positive. Three participants did not want to know their HIV status and they were left out of further analyses. The median age of HIV-positive participants was 41 years (IQR 34–49), which was significantly higher compared to that of HIV-negative participants (35 years [IQR 31–40]; Mann Whitney U-test: $p < 0.001$). HIV-negative participants had significantly more often received high-level education (83%) compared to HIV-positive participants (70%) ($p = 0.007$). During the first visit that included HCV questions, HIV-positive participants significantly more often reported risk behaviour associated with HCV transmission compared to HIV-negative participants; e.g., unprotected passive anal intercourse with a casual partner (70% versus 31%, $p <0.001$), passive fisting with a casual partner (12% versus 4%, $p=0.006$), group sex (41% versus 30%, $p = 0.042$), and recreational drug use (cocaine and/or XTC and/or poppers and/or special K (Ketamine) and/or GHB and/or amphetamines and/or methyl amphetamines) (69% versus

53%, p = 0.004). Between October 2008 and January 2010, 88% (477/539) of participants filled out the same HCV questionnaire for a second time. Of these, 401 were still HIV negative, 69 had already been HIV positive the first time, and 7 had seroconverted between the first and second questionnaire. These seven seroconverters were left out of further analyses when comparing the first and second questionnaire, since change in HIV status may influence behaviour and knowledge. The median time between fulfilment of the first and second questionnaire was 1.0 year (IQR 0.97–1.08).

Awareness of HCV

In the first visit that included the HCV questions, 70% (312/444) (95% CI = 66–74) of HIV-negative participants and 80% (74/92) (95% CI = 71–88) of HIV-positive participants reported to be aware of HCV. In univariate analyses, both HIV positivity (OR 1.74, CI 95% 1.00–3.03) and engaging in group sex (OR 1.58, CI 95% 1.03–2.42) were significantly associated with being aware of HCV (Table 1). In multivariate analysis, the odds of being aware of HCV were still higher for participants reporting group sex, but this effect became borderline significant.
In the second wave, approximately one year later, 60% (9/15) of HIV-positive participants, who had been unaware of HCV at the first survey, became aware. Of HIV-negative participants, 59% (70/119) of those unaware became aware. Overall, awareness increased from 72% in the first visit to 81% in the second visit ($p < 0.001$). Having had sex with casual partners compared to not having had sex with casual partners, was, in univariate analyses, significantly associated with becoming aware of HCV in the period between the first and second visit (Table 2). Since no other (uncorrelated) determinants were significantly associated with becoming aware in univariate analyses, no multivariate analysis was performed for this outcome.

Reported HCV testing and awareness of HCV treatment

In the first survey, 74% (55/74) of those HIV-positive participants who were aware of HCV reported that they had been tested for HCV. Of them, 18% (10/55) reported to have been tested positive, which could be confirmed for 6/10 persons who had positive test results from earlier HCV-antibody screening in the cohort. Of the HIV-negative participants that reported to have been tested for HCV (35% = 107/310), 98% (104/106) reported a negative HCV-status and 2% (2/106) did not know their HCV-status. Of the 222 persons who reported they had not been tested or did not know if they had been tested before, 97 (44%) answered that they had been tested when asked one year later in the second survey. Awareness of the existence of HCV treatment was slightly lower among HIV-negative participants (55% = 171/309) compared to HIV-positive participants (63% = 45/72) although not significantly (p=0.27). Overall, the awareness of treatment improved in the second survey; 11% of HIV-negative (p<0.001) and 17% of HIV-positive participants (p=0.035) unaware of treatment in the first visit reported to be aware of treatment in the second visit.

Table 1. Variables associated with HCV awareness as reported in first questionnaire in univariate and multivariate logistic regression analyses, among HIV-positive and -negative MSM of the Amsterdam Cohort Studies (n=536).

Determinants reported in first questionnaire	Aware of HCV	Univariate analysis			Multivariate analysis		
All	**72% (386/536)**	**OR**	**95% CI**	**p-value**	**OR adjusted**	**95% CI**	**p-value**
HIV status				0.05			0.21
Seronegative	70% (312/444)	1			1		
Seropositive	80% (74/92)	1.74	1.00-3.03		1.45	0.82-2.58	
Age in years				0.108			0.19
<33	67% (122/183)	1			1		
33-39	73% (145/198)	1.65	1.02-2.68		1.56	0.94-2.58	
≥39	77% (119/155)	1.21	0.74-1.97		1.16	0.69-1.92	
Education				0.54			
Low	69% (66/96)	1					
High	72% (294/409)	1.16	0.72-1.88				
Sex with casual partners in the previous 6 months				0.57			
No	71% (93/132)	1					
Yes	73% (289/396)	1.13	0.73-1.75				
Unprotected passive anal intercourse with casual partner(s) in the previous 6 months				0.33			
No casual partner	71% (93/132)	1					
Casual partner but no passive anal intercourse	70% (110/158)	1.04	0.63-1.72				
Casual partner and protected passive anal intercourse	72% (104/145)	0.94	0.56-1.58				
Casual partner and unprotected passive anal intercourse	80% (72/90)	0.60	0.32-1.13				

Table 1. Continued.

Determinants reported in first questionnaire	Aware of HCV	Univariate analysis			Multivariate analysis		
All	**72% (386/536)**	**OR**	**95% CI**	**p-value**	**OR adjusted**	**95% CI**	**p-value**
Passive fisting with casual partner(s) in the previous 6 months				0.42			
No casual partner	70% (93/132)	1					
Casual partner but no passive fisting	72% (257/355)	2.38	0.66-8.57				
Casual partner and passive fisting	85% (17/20)	2.16	0.62-7.54				
Group sex in the previous 6 months				0.04	1	0.97-2.30	0.07
No	69% (249/359)	1			1.49		
Yes	79% (132/168)	1.58	1.03-2.42				
Number of partners during group sex in previous 6 months*				0.10			
No group sex	69% (249/359)	1					
2 or 3 partners during group sex	76% (69/91)	1.83	1.00-3.35				
More than 3 partners during group sex	81% (62/77)	1.32	0.63-2.76				
High-risk sexual behaviour in the previous 6 months**				0.30			
No	72% (210/293)	1					
Yes	76% (148/195)	1.25	0.82-1.89				
Drug use*** in the previous 6 months				0.30			
No	70% (164/235)	1					
Yes	74% (218/295)	1.23	0.84-1.79				

Notes: *This variable was not included in multivariable analysis because of correlation with the dichotomous group sex variable.
**High risk sexual behaviour defined as: unprotected passive anal intercourse with casual partner and/or passive fisting with casual partner and/or group sex with > 3 casual partners.
***Drug use defined as use of: cocaine and/or XTC and/or poppers and/or special K and/or GHB and/or amphetamines and/or methylamphetamines (overall and/or during sex).

Table 2. Variables associated with becoming aware of HCV in univariate analysis, among HIV-positive and -negative MSM of the ACS reporting to be unaware of HCV in the first questionnaire (n=134)

Determinants reported in second questionnaire	HCV unaware in first visit and aware in second visit	Univariate analysis		
All	**59% (79/134)**	**OR**	**95% CI**	**p-value**
HIV status				0.93
Seronegative	59% (70/119)	1		
Seropositive	60% (9/15)	1.05	0.35-3.14	
Age in years				0.24
<33	49% (19/29)	1		
33-39	60% (33/55)	2.19	0.88-5.44	
≥39	68% (27/40)	1.39	0.59-3.25	
Education				0.26
Low	50% (13/26)	1		
High	62% (64/103)	1.64	0.69-3.90	
Sex with casual partners in the previous 6 months				0.02
No	44% (17/39)	1		
Yes	65% (62/95)	2.43	1.14-5.20	
Unprotected passive anal intercourse with casual partner(s) in the previous 6 months				0.09
No casual partner	44% (17/39)	1		
Casual partner but no passive anal intercourse	66% (35/53)	5.18	0.97-27.60	
Casual partner and protected passive anal intercourse	58% (18/31)	2.06	0.40-10.72	
Casual partner and unprotected passive anal intercourse	80% (8/10)	2.89	0.53-15.91	

Table 2. Continued.

Determinants reported in second questionnaire	HCV unaware in first visit and aware in second visit	Univariate analysis		
All	**59% (79/134)**	**OR**	**95% CI**	**p-value**
Group sex in the previous 6 months				0.39
No	58% (59/102)	1		
Yes	67% (20/30)	1.46	0.62-3.43	
Number of partners during group sex in previous 6 months				0.76
No group sex	58% (59/102)	1		
2 or 3 partners during group sex	65% (11/17)	1.46	0.41-5.15	
More than 3 partners during group sex	67% (8/12)	1.09	0.23-5.19	
High-risk sexual behaviour in the previous 6 months*				0.81
No	57% (44/77)	1		
Yes	67% (26/39)	1.10	0.50-2.42	
Drug use** in the previous 6 months				0.14
No	52% (32/62)	1		
Yes	64% (45/70)	1.69	0.84-3.39	

* High risk sexual behaviour defined as: unprotected passive anal intercourse with casual partner and/or passive fisting with casual partner and/or group sex with > 3 casual partners

** Drug use defined as use of: cocaine and/or XTC and/or poppers and/or special K and/or GHB and/or amphetamines and/or methylamphetamines (overall and/or during sex)

The majority of participants considered HCV infection to be a severe (44%) or very severe (39%) disease, with HIV-positive participants slightly more often considering it to be very severe than HIV-negative participants (50% versus 36%, p=0.11).

Knowledge of HCV transmission and complications

The knowledge of HCV transmission and complications in the first and second visit is presented in Figure 1 and Table 3.

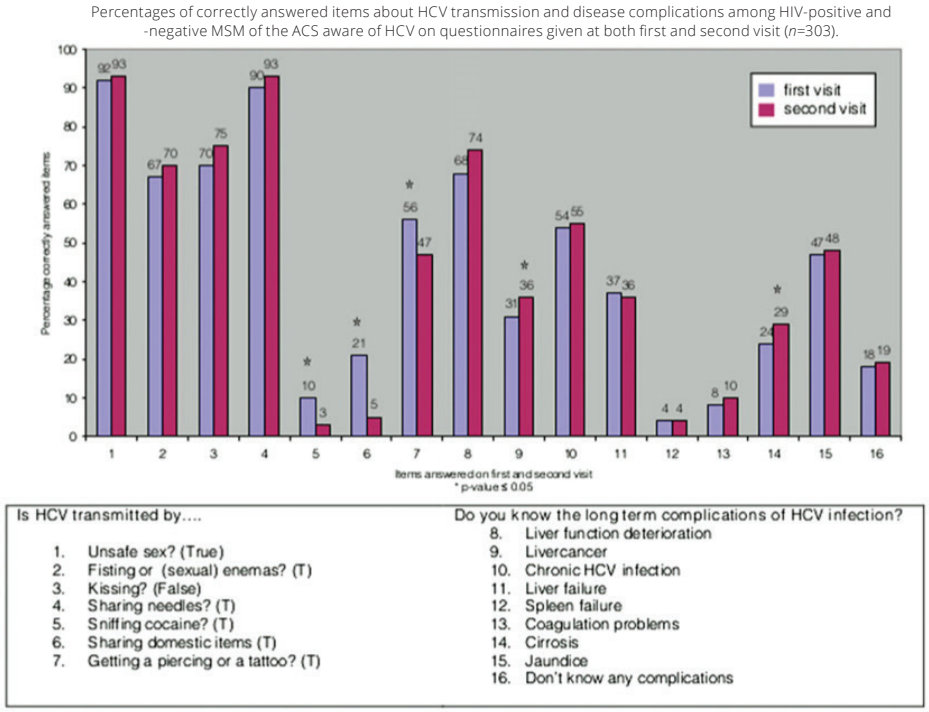

Figure 1. Percentages of correctly answered items about HCV transmission and disease complications among HIV-positive and -negative MSM of the ACS aware of HCV on questionnaires given at both first and second visit (n=303).

Overall, in the first visit, the majority of participants correctly answered the questions regarding HCV transmission. The number of persons reporting that HCV transmission occurs through domestic items and sniffing cocaine was limited and decreased inbetween visits. The transmission of HCV through unsafe sex and fisting, which are considered the foremost determinants of HCV infection in MSM, was reported as known by, respectively, 92% (unsafe sex) and 67% (fisting) of participants.

However, the complications of HCV infection were less well known. Specifically, the knowledge that liver cancer (31%) and liver failure (37%) are complications of HCV was remarkably low. Although in the second visit the knowledge of some complications improved significantly (see Table 3), most complications remained unknown for 50% of participants or more.
HIV-positive participants significantly more often reported that sniffing cocaine is associated with HCV transmission compared to HIV-negative participants (17% versus 7%, $p = 0.048$). HIV-positive participants more often knew that chronic infection and cirrhosis were complications of HCV-infection than HIV-negatives did (data not shown, all p values < 0.05). Notably, among those who were aware of HCV, there were no significant differences in knowledge between participants with and without high-risk sexual behaviour, regardless of HIV status (data not shown).

Table 3. Percentages of correctly answered items about HCV transmission and disease complications among HIV-positive and -negative MSM of the ACS aware of HCV on questionnaires given at both first and second visit (n=303).

	First visit	Second visit	p-value*
Is HCV transmitted by....			
Unsafe sex? (True) *Yes*	92% (271/296)	93% (271/292)	0.74
Fisting or (sexual) enemas? (T) *Yes*	67% (197/294)	70% (202/289)	0.28
Kissing? (False) *No*	70% (199/286)	75% (215/286)	0.11
Sharing needles? (T) *Yes*	90% (260/288)	93% 269/290)	0.36
Sniffing cocaine? (T) *Yes*	10% (27/282)	3% (9/287)	0.001
Sharing domestic items (T) *Yes*	21% (58/282)	5% (14/285	<0.001
Getting a piercing or a tattoo? (T) *Yes*	56% (161/290)	47% (134/287)	0.04
Mean total score:	4.2 out of 7	3.4 out of 7	<0.001
Do you know the long term complications of HCV infection?			
Liver function deterioration *Yes*	68% (207/303)	74% (224/303)	0.08
Livercancer *Yes*	31% (93/303)	36% (110/303)	0.05
Chronic HCV infection *Yes*	54% (164//303)	55% (168/303)	0.74

Table 3. Continued.

	First visit	Second visit	p-value*
Do you know the long term complications of HCV infection?			
Liver failure *Yes*	37% (112/303)	36% (108/303)	0.75
Spleen failure *Yes*	4% (13/303)	4% (13/303)	1.00
Coagulation problems *Yes*	8% (24/303)	10% (29/303)	0.36
Cirrosis *Yes*	24% (72/303)	29% (88/303)	0.04
Jaundice *Yes*	47% (141/303)	48% (145/303)	0.75
Don't know any complications *Yes*	18% (54/303)	19% (57/303)	0.78
Mean total score:	2.8 out of 8	3.0 out of 8	0.006

* The McNemar test was used to test differences in prevalence of individual correctly answered knowledge items between first and second visit, the paired sample t-test was used to test differences in mean total score between first and second visit

Discussion

This prospective study of MSM in the ACS demonstrates that HIV-positive MSM, the persons most at risk for HCV transmission in this population, are well aware of HCV.

Remarkably, the difference in awareness of HCV between HIV-positive and -negative participants is small. Several explanations may be given for this fact. The fear for further spread of infection from the HIV positive to the HIV-negative population might be high and therefore driving the spread of awareness among all MSM. Also, the media through which information on HCV is provided will also be read by HIV-negative men. Furthermore, it could be that participating in a cohort leads to more interest in this topic at forehand, or HIV-negative individuals may be less able to distinguish between different types of hepatitis and thus incorrectly state awareness of HCV. During the year of follow-up, awareness of HCV increased (by 9%) among both HIV-positive and -negative men. This may be due to the start of extended prevention messaging and increased HCV testing in the STI clinic and testing and treatment in HIV outpatient centres. Overall, knowledge of the transmission routes of HCV is rather good. Knowledge of complications of HCV is suboptimal and needs to be improved.

When specifically studying the characteristics of persons aware of HCV or becoming aware of HCV, we demonstrate that certain risk behaviours, e.g., group sex and having sex with

casual partners, are associated with awareness. Group sex characterises the group at risk of HCV and thus, we show that in the group where awareness is needed most, it is specifically present and spreading.

Even when awareness is high, knowledge of transmission routes is essential to implement preventive measures correctly. Overall, knowledge of the transmission routes of HCV is rather good. The most risky transmission routes, such as unsafe sex, fisting and needle sharing, are well known. Remarkably, the overall mean score of knowledge of transmission routes decreased over time. This is due to a significant decrease in the knowledge of the items "sniffing cocaine," "sharing domestic items," "getting a piercing or tattoo." This may be explained by communication of new insights into these HCV transmission routes in the same time period, for example that there is in fact a very low risk of HCV transmission through tattooing and/or piercing in the Netherlands [22], and a further emphasis of prevention messages on sexual transmission. Clear and specified knowledge should be provided about these less common transmission routes along with messaging that focuses on the sexual risk behaviour.

HIV-positive participants were, as expected, more aware of long-term complications of HCV than those participants who were HIV negative, but the limited knowledge of serious complications such as liver cancer and liver failure may influence the perceived threat of HCV. A diminished perceived threat may lead to less implementation of prevention measures and more risky behaviour [23]. Emphasising the longterm complications of HCV infection in prevention messages may, therefore, be a useful addition to the current information provided.

Although in our study we could not examine possible changes in risk behaviour that occurred after becoming aware, it may be worrisome that risk behaviour is reported despite awareness of HCV and knowledge of transmission routes. The recent report of a very high incidence of HCV reinfection among the MSM population in Amsterdam strongly suggests that preventive measures are indeed not implemented sufficiently [24]. If patients are well informed but do not stop at-risk behaviour, prevention strategies should be evaluated; primary prevention messages should be tailored to the attitudes and needs of the target population, and secondary prevention measures, such as enhanced HCV screening and early treatment, should be strengthened.

Furthermore, continuing attention to the HCV epidemic among MSM through targeted campaigns may lower stigma regarding HCV infection in this population. Since stigma may be a barrier for men to participate in peer education, a successful method in promoting healthy behaviour, knowledge about HCV may remain suboptimal [25]. Even when knowledge of HCV is present, mental health problems such as depression or drug use could hamper the implementation of knowledge of HCV transmission [26]. Making these issues part of a campaign may support MSM in comprehending and changing risky behaviour.

Although no HCV-prevention materials were provided at the ACS study site, when evaluating the change in awareness and knowledge over time we realize that there may be a cohort effect, i.e., a learning effect of the baseline questionnaire. Although this effect cannot be differentiated from an actual effect of calendar time, it is still meaningful to monitor the change in awareness and knowledge in order to evaluate and adapt prevention strategies. Moreover, if increase in knowledge is due to this learning effect within the cohort, it could be considered encouraging that even minimal attention can lead to change in knowledge.
There are some study limitations. First, the ability of participants to distinguish between hepatitis A, B and C was not measured and might have influenced the answers and results. Second, this study represents the results of a cohort of HIV-positive and -negative MSM and therefore we need to be careful when generalising results to the total population of MSM in Amsterdam.

In conclusion, awareness of HCV is high among MSM in the ACS. Specifically, HIV-positive MSM and MSM reporting group sex, an important determinant of HCV infection, are highly aware and knowledgeable about HCV transmission. However, since the knowledge of complications of HCV infection in particular is limited, more specific messages concerning these complications may influence risk perception and behaviour. New campaigns should be targeted specifically to HIV-positive MSM and HIV-negative MSM who engage in risky behaviour, such as unprotected sex with HIV-positive or HIV-unknown casual partners. For those with persistent high-risk behaviour, secondary prevention that includes regular HCV screening should be implemented and encouraged.

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Chapter 4.3

Changing the odds: motives for and barriers to reducing HCV-related sexual risk behaviour among HIV-infected MSM previously infected with HCV

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Abstract

Background

Among HIV-infected MSM who have been treated for HCV infection, the HCV reinfection rate is high. It is therefore essential to understand their perceptions of HCV risk behaviour and risk-reducing strategies.

Methods

This qualitative study among 20 HCV-infected MSM, the majority treated in the era before direct acting antivirals, provides insight into their ideas, motives, and barriers concerning HCV risk reduction, and aims to strengthen prevention strategies for both primary HCV infection and HCV reinfection.

Results

The strongest motive to implement risk reduction strategies was the reward of avoiding HCV retreatment and its side effects, but this may change with the current implementation of less burdensome HCV treatment. Also, the sexual risk norms in the MSM scene, including social pressure towards risk-taking, HCV stigma, and non-disclosure of HCV status, all form barriers to safe sex. Drug use, strongly present in the context of clubs and group sex, directly impedes the self-efficacy of men to take risk reduction measures.

Conclusions

Tailored prevention messages, empowerment of self-efficacy for risk reduction, and more insight into risk behaviour over time are ingredients for effective HCV prevention among these men.

Background

The emergence of an epidemic of hepatitis C virus (HCV) infections among HIV-infected men who have sex with men (MSM) has become a new public health problem in high-income countries [1, 2]. Previously, the transmission of HCV, a bloodborne virus, was exclusively related to injecting drug use, surgical procedures, or usage of contaminated blood products. Studies among heterosexuals found the risk for sexual transmission of HCV to be extremely low [3]. Prevention of HCV infection was therefore focused on harm reduction strategies such as needle exchange programs, methadone provision, and screening of blood products [4]. However, the main risk factors for HCV transmission in HIV-infected MSM appear to be sexual [2]. Several studies have demonstrated that sexual practices such as fisting and sharing of toys, but also unprotected anal intercourse, specifically in a group-sex setting and under influence of drug use, are associated with acute HCV infection among HIV-infected MSM [5-7]. Unlike HIV infection, HCV infection can be cleared spontaneously or, in the last three decades, by increasingly successful treatment [8-10]. Until 2011, treatment of HCV consisted of weekly peg-interferon in combination with daily ribavirin, with modest success rates and side effects such as depression and anemia. Since the introduction of direct acting antivirals (DAA), it is highly successful with fewer side effects [11]. Accessibility to DAA differs according to disease stage (grade of fibrosis) and differs per country. Also, DAA is not yet approved for acute HCV infection in every country. Most important, HCV clearance does not preclude reinfection if risk exposure continues. The incidence of HCV reinfection in the HIV-infected MSM population is high, at 5–15 per 100 person-years [12-15]. This suggests that some MSM are not able to implement HCV risk reduction measures after HCV clearance. To diminish the HCV epidemic among MSM, it is necessary to understand the bottlenecks for the implementation of risk reduction strategies. It is important to understand the motives regarding the practice of HCV-related sexual risk behaviour and the motives and barriers as to application of risk-reducing strategies. Such information will help strengthen strategies to prevent both primary HCV infection and HCV reinfection. The purpose of this qualitative study among 20 MSM with previous HCV infection was to provide this much-needed information.

Methods

Recruitment and sample

The study is based on in-depth interviews held from January 2011 to December 2012. In total, 19 HIV-infected MSM who were HCV-coinfected, plus 1 HCV mono-infected MSM were interviewed to gain insight into their motives and barriers as to implementation of HCV risk reduction strategies. Men were recruited from the 'MSM Observational Study of Acute

Infection with hepatitis C' (MOSAIC) at several HIV outpatient clinics or through the HCV facebook page of 'Poz and Proud,' a subcommittee of the HIV Organization Netherlands, a non-governmental organization which works in the interests of persons infected with HIV. Written information on the study was provided by the HIV nurse or study coordinator at recruitment. If men chose to enroll, they were invited by phone or email for an interview at their regular HIV-treatment location or at the offices of the Public Health Service of Amsterdam, depending on their preference. Recruitment continued until data saturation was reached, i.e. until no new motives or barriers to reducing sexual risk behaviour and using risk reduction strategies emerged during the interviews.

Procedure

In total, 20 face-to-face in-depth interviews, one per participant, were conducted (average duration: 60–75 min) by a medical anthropologist trained in qualitative research methods. At the beginning of each interview, the participants were provided with information on the aim of the study and the established conditions for anonymity and confidentiality, followed by an oral informed consent. The interviews were semi-structured and allowed the interviewer to deeply explore the participant's feelings and perspectives on the relevant subjects.
The main focus concerned the impact of sexually-acquired HCV infection on sexual risk-taking and the motives and barriers to reducing risk behaviour. A topic list (Table 1) was used to initiate rapport between interviewer and participant, and themes were developed according to participant disclosures. The interviewer was free to pursue areas of interest or to probe responses further for clarification. All interviews were audio-taped and transcribed verbatim. Participants received a gift certificate (€20) for their participation.

Theoretical background

The Protection Motivation Theory was used as a theoretical base for the interpretation of the data. Protection motivation refers to the motivation to protect oneself against a health threat like an HCV infection. The theory proposes that the intention to protect oneself depends upon two concepts. One consists of the *threat appraisal* of a disease, in this case HCV infection: its perceived *severity*, one's perceived *vulnerability* (probability of becoming infected), and the perceived *rewards* of implementing preventative measures. The other concept consists of the *coping mechanisms* for implementing protective measures: the perceived *response efficacy* of the measures (the belief that they are truly preventative), the perceived *self-efficacy* (the belief that one is able and likely to perform the preventative measures), and the *costs* of their implementation [16]. The probability of implementing HCV risk reduction strategies increases with higher perceptions of HCV severity, one's vulnerability to HCV reinfection, response efficacy, self-efficacy for implementing the strategies, and rewards of preventative behaviour. When one or more of these perceptions/factors is low, behavioural change to protect against HCV reinfection is less likely to occur.

Table 1. Main themes from topic list used during interviews with 20 (previously) HCV-infected MSM in the Amsterdam area from January 2011 to December 2012

Circumstances of HCV diagnosis	- Knowledge about HCV prior to diagnosis - Sexual behaviour prior to diagnosis - Feelings about HCV diagnosis
HCV infection	- Current HCV status - Perception of HCV since diagnosis - Experiences with treatment of HCV - Knowledge about reinfection
Sexual behaviour	- Current sexual behaviour - Sexual behaviour between diagnosis and treatment - Sexual behaviour during HCV treatment - Sexual behaviour after HCV treatment
Risk reduction strategies	- Risk reduction strategies prior to HCV infection - Risk reduction strategies after HCV infection - Influences of HCV infection on risk reduction - Perception of HCV risk in future - Perception of self-efficacy of risk reduction

Analysis

The transcribed interviews were entered into a database for coding, using qualitative data analysis software (MAXQDA 10) which allowed for coding of data segments using a flexible set of categories. In the first phase of data analyses, open coding by two researchers (a medical doctor and a medical anthropologist) was performed to explore the subjective experiences of the participants regarding HCV diagnosis, treatment, sexual behaviour, risk reduction, etc. Transcripts were repeatedly examined to discover emerging themes which were discussed and, if found relevant, added to the initial topic list of the interviews. This iterative method allowed us to adjust data collection according to what was learned [17] and ultimately to establish saturation. The two researchers coded the same data from all transcripts to ensure that codes being used were the best fit for the segments. Where disagreements were noted, they discussed their difficulties, clarified their opinions, and agreed to a final classification after discussion with the study supervisor, a social and clinical psychologist. Upon reaching consensus, the researchers continued to perform coding to excerpt and sort segments of data into subcodes. In the second phase of analyses, focussing on the research aim, the researchers grouped relevant codes into categories based on the theoretical background of the Protection Motivation Theory. They produced a list of categories covering motives and barriers to changes in sexual behaviour for use in analyzing the remaining transcripts. This procedure was followed until a definite database was created containing a definite list of categories. The final results, interpretations, and conclusions were based on that database and supported by quotes from the interviews.

Ethical framework

This study is part of the MOSAIC study which is approved for by the Medical Ethics committee of the Academic Medical Center in Amsterdam, the Netherlands.
Information on the aims, procedures, and use of findings was provided to each participant. Participants were informed that answering the interview questions was voluntary and they could withdraw from participation at any time. During the consent process, participants were informed about the confidentiality of transcripts and publications and assured that all identifying markers would be removed. The consent was recorded on audiotape and documented by transcription together with the interview.

Results

Characteristics

Participants' average age was 39 years (range 27–59), most were born in the Netherlands (95%), and approximately half of the men were in a steady relationship. Of the 20 participants, 5 were still undergoing HCV treatment during the time of the interview; 11 had been successfully treated in the (recent) past; 2 had been unsuccessfully treated and were chronically infected; 1 was chronically infected and had never received treatment, and 1 had spontaneously cleared the HCV virus. Of the 5 in treatment, 4 men had contracted HCV more than one time: 2 had been reinfected once, and 2 had been reinfected for the second time.

Interview results

First, we will describe the risk reduction strategies that were implemented by the participants, followed by the motives and barriers to changing sexual risk behaviour and applying HCV risk reduction strategies.

Implemented HCV risk reduction strategies

Participants described a wide range of strategies used to prevent HCV reinfection.

Preventing direct transmission

Several strategies concern reducing direct transmission of HCV during sex, e.g. using condoms; not sharing gloves, toys or lubricant; and limiting mucosal damage:

> "No sharing of gloves, condoms, toys, et cetera (….), surely these kind of essential things, which may give blood-to-blood contact (…..). Well, using a toy or something like that, while being with more persons at the same time, it could happen that we

exchanged it. But now [after HCV diagnosis] I'm very cautious that this won't happen to me again." (MSM5).

"Sometimes Crisco [lubricant] is being used. So then you should be using your own jar. If you go through it [Crisco] and then someone else goes through it, you could just as well have unsafe sex." (MSM4).

"Using drugs anally is something I definitely don't do anymore (...). I suspect it is unhealthy for the mucosa, by which you increase the risk of being more susceptible to not only HCV but also other STI." (MSM8).

HCV serosorting

Some strategies to diminish risk of reinfection depend on choosing sex partners based on their assumed HCV status:

"When someone is HCV-infected, I don't want sex with him. Just because of the risk of infection." (MSM11).

"Well, we still have unsafe sex with each other, but not at the moment, because he is HCV-infected and I absolutely don't want to become infected again." (MSM5).

Avoiding risk-related contexts

Some risk reduction strategies involve simply trying to avoid specific sexual contexts that are perceived by participants as encouraging risk. Group sex, sex in clubs, or sex under influence of drugs are perceived as contexts associated with risk-taking:

"During group sex at a club, you are more likely to meet somebody with HCV, because you have sex with more men. Also it is more likely to skip the use of a condom, especially near the end of the evening after four glasses of vodka. So I am eliminating that kind of group sex at those clubs. I am going one-on-one. That lowers the risk of contracting HCV." (MSM19).

"I think drugs are a risk factor anyway, and that is why I would like to eliminate them." (MSM11).

"I'm totally done with drugs. You know, I can say that drugs were partly the cause, and that's true, but in the end I myself am responsible for my actions. So I did it myself.

So I don't want to blame it all on drugs, but drugs have certainly been a catalyst. If I hadn't used it, I would have certainly used a condom during sex." (MSM17).

Being cautious on the internet
Negotiating safe sex with partners met through internet dating is perceived to be challenging, as disclosure of HIV and HCV status and safe-sex intention are sometimes not apparent or transparent over the internet. Some men are therefore more cautious when dating through the internet or using the information put online to screen their choices:

"I will never date somebody who fills in 'needs discussion' [answer to question about safe-sex intention on internet profile], because that means that they do not always have safe sex. And I can't trust them, especially when drugs are involved." (MSM18)

"*Do you make new contacts through the internet?*" *(interviewer).*
"We really don't feel like that anymore. We think that world can't be trusted. They never say what's going on, what they have. That risk is too big for us. You never know what you get into your home. No, we don't do that anymore." (MSM2).

Motives for implementing risk reduction strategies

Effect of diagnosis and treatment on sexual desire and self-perceived attractiveness
Men reported changing behaviour shortly after start of HCV treatment due to its impact on sexual desire. Many men suffered from side effects such as extreme fatigue, flulike symptoms, and depression which lowered sexual desire and the ability to take sexual initiatives. Reducing sexual behaviour during treatment could therefore be not so much driven by deliberate rational or emotional motives but rather by physical circumstances:

"The medication is heavy, I agree; because of that you don't have sex anymore, you don't feel like going out, you don't do any drugs. So, the medication is heavy, but the choices you have to make are actually made for you, which is very easy. But what happens when you have finished the treatment?" (MSM5).

"You get a lot of side effects, you feel really sick, every weekend again, so you won't be able to do a thing." (MSM15).

Moreover, men feel too unattractive to have sex, partly due to the stigma of HCV infection:

"*Did the HCV diagnosis influence your sexual life? You mentioned that at the beginning you did not feel like it [having sex].*" *(interviewer).*

> "Well, I felt dirty. You know, dirty not in a sense that nobody was allowed to touch me but, well, there is quite a taboo against HCV. It is also being called the new HIV, comparable to some years ago. HIV is sort of seen as something normal, but HCV is not." (MSM6).

Fear of HCV treatment side effects

Almost all participants perceive HCV to be a severe infection, like or even more severe than HIV infection or other STI. This is mainly due to the negative perception of HCV treatment. As stated above, HCV treatment side effects have a strong impact on physical and mental health and day-to-day life, including work, social life, and relationships, and are therefore mentioned as an important motive for behavioural change:

> "Well, you see, I always say I would a hundred times rather have an HIV infection than an HCV infection, and I really mean it. Because HIV really means nothing compared to it [HCV]." (MSM9).

> "That's what [HCV] changed my behaviour. You see, an infection with gonorrhea or chlamydia sometimes means taking a pill, not a treatment you want very often, but it's not a disaster when it sometimes happens. But this [HCV] is really something that has great impact and simply takes six or, when unlucky, twelve months of your life. It's not worth it." (MSM5).

> "It is such a demanding treatment, if I were to go through it again, I fear things might go wrong. I simply don't want that to happen. So from now on I do it safe or not at all." (MSM3).

Fear of infecting others

In addition, an often mentioned motive for changing behaviour is the fear of infecting somebody else:

> "Both times that I was HCV-infected I did not have sex during the treatment period… [tells reasons]. I also wanted to be sure that I did not infect anybody with HCV." (MSM19).

Knowledge and high perceived susceptibility

The fear of becoming infected yourself is related to the perceived personal susceptibility for HCV infection. For some, experiencing previous infection and subsequently gaining knowledge about transmission has increased the perceived susceptibility for a new infection and contributed to changing behaviour in the future:

> "Well, on the other side, I wasn't totally aware how easy you can become infected with HCV. I always assumed you really had to do a lot: so really have rough sex or long-lasting sex, you know, that there really should be blood. That's what I thought, about the way you get HCV through sex, and that's not what I did. Now that I know that the HCV virus can stay alive outside your body for a long time, it becomes a whole different story (...). If I had known that back then, I would not have done that." (MSM11).

Barriers to implementing HCV risk reduction strategies

Although most participants were motivated to implement one or more of the above-mentioned risk reduction strategies, a wide range of barriers to do so was mentioned.

Lack of HCV knowledge and low response efficacy

The intention of implementing risk reduction strategies may be absent or hampered when the participant does not know how HCV transmission can be prevented or does not believe in the efficacy of preventative strategies:

> "Well of course you have this idea, you can contract anything, when you don't know how you contract it, you can't prevent it anyway. I might better live in a bubble then. I mean, you can't protect yourself if you don't know what to protect yourself against. It's no use." (MSM7).

> "I should stop having any sex at all, because it really doesn't matter what I do to prevent HCV. Whether I am having safe sex or not, I will contract it either way." (MSM19).

Heat of the moment

Sex has been described as a non-rational act that does not always line up with considering and actively introducing protective measures in the heat of the moment:

> "It's like, postponing thinking about the possible consequences at the moment you have sex; the heat of the moment, but also thinking that you won't catch it again. Afterwards, you naturally think 'how stupid of me'." (MSM19).

Negative impact on sex quality

The use of condoms can negatively influence an erection, and is therefore an obstacle to performing sex:

> "With a condom, it's always difficult and because it's a hassle, you lose your erection. It makes me nervous because I'm not used to it." (MSM 11).

Challenging settings

Certain sexual contexts, such as club settings or group sex are described as having an impact on the capability to use condoms or implement other risk reduction strategies:

> "Sometimes I go to certain clubs. It's much easier there to let go of certain things and to be less careful than you normally are (…). It's the group process and also exhibitionism, to a certain extent." (MSM19).

> "(…). sometimes such a party goes on for two days and at a certain point people just go on, and things get a bit, well, messy: a hand goes in or a dildo, I don't know. Thinking becomes less sharp." (MSM17).

> "No, you're not with the same partner the whole evening. It happens, but mostly not. No, four, five, six….At a certain point, hands don' t get washed that well anymore." (MSM12).

Drug use

Drug use was reported to lead to impulsivity and to impede the ability to consistently implement risk reduction strategies.

> "*During which situations did it [safe sex] go by the board?" (interviewer).*
> "When you're under influence of drugs, I would say. You become less careful, you're not really aware anymore." (MSM2).

Sexual risk habits and peer pressure

A commonly mentioned barrier is the habit of not using condoms when those around you are not using them either. Many men became part of the "bare-scene" after having been diagnosed with HIV. They became used to not needing a condom anymore to prevent HIV infection. Breaking that norm by re-starting condom use to prevent HCV-infection proves to be difficult:

> "In a very short period, the behaviour of many people changed [to bare sex], including mine."
> *Do you have an explanation for that?*
> "Yes, I do. Firstly I think that at a certain moment it's almost strange to use a condom if everybody does it [bare sex]. That's because the risks and the quality of [HIV] treatment have improved. It's kind of backwards: just because you know that your life is not (or less) at stake, you start taking more risks." (MSM5).

"Every person that's [HIV] positive, in my surrounding, does it unsafe."
"*So, unsafe sex is actually the norm?*"
"Yes, for positive persons it is." (MSM6).

"It's not like just using a condom again, it's a total switch in your behaviour." (MSM14).

Disclosure-related barriers
Being part of a sex environment that does not use condoms also leads to the fear of losing sexual partners when making HCV infection and condom-use part of sexual negotiation, as this necessitates the disclosure of the HCV status. Participants confirmed that disclosure of HCV status is therefore complicated and often not done:

"It's not desirable to contract HCV, certainly not since most are already HIV-positive. They feel like, 'That's something I can't handle [on top of HIV] as well, and I won't tell it once I have it.' It's like that for me, because I don't tell it either. I feel like, no one is talking about it, why should I? If I would, I know for sure that I won't receive any invitations [for sexual contact] anymore." (MSM17).

In addition, for men who have not disclosed their HIV status, the disclosure of HCV status can mean two disclosures at once:

"When someone hears hepatitis C and starts googling it, then it becomes evident that the person in question is also HIV-positive [...] That feels like a nasty blow. I thought, I'm doing it the wrong way, I should not disclose it this easily." (MSM18).

Open disclosure of HIV or HCV status online occurs often. The internet is a low-threshold way to meet sexual partners and is often used by MSM. Statements about wanting to have safe sex only or about one's negative HIV/HCV status are sometimes visible on online user profiles. However, study participants have experienced that these statements are not always trustworthy:

"It's not like, when somebody says safe sex [preferred type of sex expressed on the internet profile], it will automatically be like that." (MSM5).

"Well, then [when posting you want condomless sex] you actually show you are HIV- seropositive. Consequently you also sort of admit you are HCV-positive. So, you actually contradict your own status. Many rather not do that. So, you post 'safe'." (MSM17).

> "On the other side, I have also had a chat session with somebody literally asking me 'you don't have an STI?' My thoughts at that moment were: I'm not going to tell you I have HCV, I don't even know you. I mean, you will pull out, but what will you do with that information? You've got my chat name, perhaps we have contacts in common, so it's easy to blab to others about it.
> "*So what did you do?*" (interviewer)
> "I told him I did not have anything." (MSM18).
> "*And you met up with him?*" (interviewer).
> "Yes." (MSM18)
> "*And the subject was not brought up again?*" *(interviewer)*
> "No." (MSM18)
> "(.....) *So, it's difficult to make it open to discussion?*" *(interviewer).*
> "Yes, it's really very complicated." (MSM18).

Mental health

Some men reported their ability to implement risk reduction was influenced by their mental condition. Symptoms of depression are described as posing another barrier for implementing risk reduction strategies:

> "(...) when you care less about yourself, (...), a sort of neglect [takes place]. That's in fact what in a way also happened to having safe sex." (MSM 16).

Declining perceived severity due to decline of side effects

When treatment has been successful, the motivation to prevent HCV reinfection may decline due to the fact that the experienced discomfort declines:

> "I mean, the first months [after HCV treatment] you start feeling better and you have good intentions; it's not going to happen to me again. But I know what I'm like. At a certain moment, when it's a year later, you start crossing your boundaries again, doing this and that." (MSM5).

Discussion

The main focus of this study concerns the impact of sexually acquired HCV infection on sexual risk behaviour among HCV-infected MSM, exploring which risk reduction strategies are being implemented and what are the motives for and barriers to their implementation.

We will discuss our results within the theoretical framework of the Protection Motivation Theory and existing literature. Accordingly, we will suggest strategies to improve interventions for MSM with and at risk of HCV (re-)infection.

Threat appraisal of HCV infection

Severity

In contrast to another qualitative study [18], possible complications of HCV infection such as chronic liver disease and its maligne interaction with HIV infection did not profoundly contribute to the perceived threat of HCV among our participants. It could be that the fear of complications was not specifically mentioned during the interviews because other topics, such as the severity of HCV treatment, were more salient. It could be that expectations of favourable treatment outcome are predominantly high. For treatment with peg-interferon and ribavirin, starting treatment shortly after diagnosis of acute HCV, the success rate of HCV treatment is indeed high, even in HIV-coinfected patients [19]. As a result, men perhaps do not perceive the severe consequences of untreated HCV infection as a likely scenario for their future, considering their high intention to get treated. Still, when treatment fails, complications such as liver cirrhosis can become severe and may occur more quickly as suggested by Fierer et al. [20]. Finally, our participants may simply be unaware of HCV complications, as was found among MSM participating in the Amsterdam Cohort Studies [21]. Addressing complications of HCV infection in the at-risk population through HCV-specific information campaigns can contribute to more accurate threat appraisal. Particularly when information is provided by HCV-infected peers, the consequences of infection may become more explicit and recognizable.

As the success rates of treatment are increasing with the introduction of new anti-HCV agents, physicians should clearly discuss with their patient the still possible side effects, the risk of reinfection and how to address it and, if relevant, the effort and financial cost that are involved.

Vulnerability

Besides the perceived severity of a disease, the perceived vulnerability to that disease determines the threat appraisal and accordingly the behavioural response.

Some of our participants did not perceive themselves as belonging to a high-risk group since they did not engage behaviour that they considered risky, such as group sex or techniques such as fisting. The emphasis of study results and prevention messages on the extremes of risky sexual behaviour as a main cause of infection seems to have anchored the feeling that *only* such behaviours can lead to HCV-infection. For some men, the fact that their infection occurred despite the avoidance of such extremes caused them to doubt the

efficacy of certain risk reduction strategies. Consequently, while some men became more careful and started implementing more rigorous risk reduction strategies, some felt there are no realistic behavioural steps they can take to make themselves any less vulnerable. Ambivalent perceptions of risk make it challenging to develop effective prevention messages. Focussing on the most risky subpopulations and highest-risk techniques may help those most at risk, but it might also create the illusion that lower-risk techniques are completely safe from HCV infection. Tailored prevention messages need to be constantly updated as the transmission dynamics within a risk population change, e.g. when HCV spreads to HIV-negative MSM, presumably because of the protective effect PrEP (pre-exposure prophylaxis) has on the acquisition of HIV [22, 23]. Furthermore, addressing only high-risk subgroups may increase the stigma around HCV and indirectly raise a barrier to risk reduction strategies, as it increases avoidance behaviour and prevents free communication and HCV status disclosure [24]. Regular consultation on preventative interventions should offer realistic messages regarding high-risk techniques and should focus on the full range of techniques that can lead to HCV infection. Discussing such techniques should be paired directly with realistic suggestions of risk reduction strategies even for techniques that are considered more low-risk.

Rewards of applying risk reduction strategies

Classic HCV treatment (peg-interferon and ribavirin) often had a temporary but severely negative effect on patients' well-being through serious physical and psychological side effects, and it consequently negatively influenced work participation, daily activities, sexual experiences and partnerships. Not wanting to go through these negative treatment-related experiences was an important motivator for behavioural change among our participants and was seen by some as an important reward for applying risk reduction strategies. Eventually though, treatment-related complaints will decline due to new less burdensome treatment options, with possibly a decline in motivation to prevent reinfection and an increase in risk-taking. Interestingly, this concern was expressed by participants themselves [data not shown]. Some expected that with new HCV treatment regimens, HCV infection will be 'just another' STI that is 'easily' treatable. Future studies should examine whether avoiding HCV retreatment is still a motive for risk reduction in the DAA-era, and close attention needs to be paid in future HCV prevention programs to the effect of new HCV treatments on declining motivation to change behaviour to avoid HCV reinfection.

Counter measures could include communication of treatment costs and the low but existing possibility of treatment failure.

An additional motive to implement risk reduction strategies was the reward of not infecting somebody else. The issue of responsibility for one's own or one's partner's health

seems affected on the one side by social commitment and, on the other side, by fear of stigmatization after status disclosure. How these conflicting forces are resolved seem to determine whether a person will or will not engage in risk reduction behaviour or status disclosure with a partner. The balance between these motives should be addressed in prevention messages for both sides of the spectrum, both to increase responsibility towards sex partners and also to decrease HCV-related stigma.

Coping appraisal of HCV risk reduction strategies

For many MSM, the barriers to risk reduction implementation are related to limited coping mechanisms for behavioural change. They question or feel challenged by both the response efficacy of risk reduction strategies and the self-efficacy of applying these strategies.

Response efficacy

To start with the response efficacy, the ongoing discussion about risk factors for HCV infection in this population apparently leaves men in doubt about what risk reduction strategies are actually effective. Some men choose to be very careful and apply all recommended strategies; others find that they still might become (re)infected even when applying these strategies. The indistinctness of risk factors leads to lack of faith in the suggested strategies and results in a perception of low response efficacy. Providing a constant, clear, and uncomplicated prevention message linked to an accessible and tailored HCV testing policy may reduce doubts about response efficacy. Using an HCV risk score to determine the need for testing, as developed by Newsum et al. [25], may be such a method.

Self-efficacy

Although low response efficacy is a major issue for some men, the majority of our participants experience barriers related to low self-efficacy. Implementing risk reduction strategies such as condom use, proper glove usage, sterilization of toys, and separate and hygienic lubricant containers is challenging in certain sexual contexts such as group sex or public venues. Helping men to improve their skills for implementing these strategies and facilitating these strategies under these conditions can improve uptake.

External factors that influence self-efficacy are difficult to tackle. In the interviews it became apparent that interpersonal interaction and situational circumstances during sex have a high impact on the self-efficacy of implementing risk reduction strategies. Since the HCV epidemic has specifically affected HIV-infected MSM, a number of our participants confirmed being part of a social network of HIV-infected MSM who practice condomless sex. They stressed that being part of this scene creates peer-based and contextual barriers to HCV risk reduction strategies that are hard to overcome. The norms and social pressure during, for example, sex parties or group sex make it more difficult to disclose HCV-status and to

request safe sex. The significance of condomless sex is multifold, ranging from pleasure-seeking to identity-forming [26, 27]. To change the norms within this social-sexual structure is challenging, but reducing HCV stigma and increasing awareness for HCV prevention within such networks is imperative. Innovative social-network approaches, e.g. using online social media and mobile phone technologies, can facilitate the dissemination of information and support within social and sexual circles and help make HCV a more overt topic of consideration.

In addition, lowering HCV testing thresholds and increasing test frequency could support men in high-risk sexual networks. For example, the development and dissemination of client-initiated HCV home-collection tests would facilitate frequent testing and distribution of tests among the high-risk networks.

Another important factor influencing self-efficacy among our participants was drug use. The percentage of HCV-infected MSM using recreational drugs before and/or during sex ("chemsex") is high [7, 28]: 84% of MSM with acute HCV who participated in the MOSAIC study compared to 53% of MSM without acute HCV. The association of HCV infection with drug use may reflect a direct transmission route of HCV through sharing needles or snorting equipment [6, 7]. However, the negative effect of drugs on self-efficacy and thereby its association with other high-risk sexual behaviour is most probable. The specific drugs used, particularly ketamine and methamphetamine, increase sexual desire and endurance, but at the same time they lessen the capability for risk assessment and behavioural adaptation. This effect was strongly emphasized by our participants. It is one of the risk behaviours that men intend to change after HCV diagnosis, but being the norm in some sexual networks, drug use is difficult to reduce. For many, it has become the only way to perform and sustain their desired sexual activity, despite the danger of slipping into generalized addictive behaviour. Changing sexually-related drug use is challenging, and emphasizing its negative consequences is not sufficient to bring long-lasting change. HCV prevention measures could perhaps integrate components of drug use interventions, such as cognitive behavioural therapy or related interventions [29, 30], into their approach. Such interventions should be tailored to the personal context and possible comorbid mental illness of the user, while also building on existing interventions [31].

The challenges that come with condom use were mentioned by our participants as a behavioural barrier to risk reduction strategies. Condom use can negatively influence their erection and impede the intimacy experienced between partners [32]. This makes them less able to use condoms, even when they intend to. However, strategies effective for increasing condom use to prevent HIV and other STI may also be effective in preventing HCV. Motivational interviewing and skills training, combined with tailored cognitive behavioural interventions, are several of these evidence-based strategies [33].

Last but not least, as described by our participants, mental health problems may also reduce self-efficacy and can be exacerbated by HCV treatment with interferon. While depressive symptoms can reduce sexual desire, they can also make one indifferent to the threat of sexually transmitted diseases. The fact that syndemic factors such as mental disorders and drug use often co-incide with high-risk behaviour among MSM [34, 35] is an issue that public health workers and physicians should bear in mind when discussing safe sex and related topics. Even though patients with depressive symptoms receive professional attention during HCV treatment, more post-treatment attention is perhaps needed and would help to prevent HCV reinfection.

Costs of applying risk reduction strategies

Some men consider the costs of changing their sexual way of life (using condoms, reducing number of sex acts, giving up group sex) as too high. For them the pleasure of sex outweighs the risk of reinfection.

Furthermore, our participants indicated that reducing risk behaviour to protect others might directly or indirectly signal their HCV and HIV positivity to old or new sexual partners, leading to rejection. This is considered one of the highest costs of implementing risk reduction strategies within the existing sexual context of our study participants. A study among MSM by Owen et al., one of two other qualitative studies on HCV stigmatization, describes its negative consequences on status disclosure and its effect on implementation of risk reduction strategies [36]. Clearly, addressing issues of HCV stigma, generating more open discourse regarding HCV transmission, and improving HCV testing and cure in high-risk MSM are more imperative than ever. Empowerment of men through interactive online training modules that allow them to practice management of disclosure issues may be one method to facilitate this.

Conclusions

With this qualitative study, we are among the first to describe the implementation of risk reduction strategies after HCV diagnosis among MSM previously infected with HCV, with emphasis on the motives and barriers to engage in such strategies. An important motive to implement risk reduction strategies was the reward of not having to go through peg-interferon/ribavirin treatment and its side effects again. This motive may lose strength in the future, as less burdensome treatments with DAA are becoming common practice. Future HCV prevention strategies should take such treatment-related changes in motivation into account. Instead of a focus on avoiding treatment, perhaps a more useful focus would be self-efficacy, since the lack of it was found to be a prominent barrier to behavioural change.

Particularly sexual norms prevalent within the sexual network of HCV-positive MSM are described as difficult to manage and result in social pressure, HCV stigma, and non-disclosure of status. Drug use, strongly present in the sexual contexts of many HCV-infected MSM, also directly influences self-efficacy. Specific training modules targeting drug use in sexual contexts should be developed, evaluated, and integrated into HCV prevention initiatives. Prevention messages should be provided on a tailored basis, considering the dynamic nature of risk behaviour and sexual networks and therefore developed and disseminated with peer cooperation, possibly using online technologies and social networking. Each HCV-positive MSM's thoughts and feelings about sexual activity, risk reduction, and HCV reinfection should be periodically explored after both HCV diagnosis and treatment to raise physician and patient awareness of possible changes in threat appraisal.

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Chapter 5

General discussion

This thesis focuses on the epidemiology, treatment and prevention of hepatitis C virus (HCV) infection in two key populations that differ considerably from each other. The first group consists of people who inject drugs (PWID), a socially vulnerable population and considered difficult to reach, serve and retain in care. Although the epidemiology of HCV infection in this group has been well described, HCV treatment uptake has overall remained limited to a small proportion of infected PWID [1]. We therefore studied factors that influence HIV and HCV treatment uptake and course among PWID, with the aim to improve accessibility and outcome of treatment in this marginalized group. The second group, a population more recently affected by HCV, consists of men who have sex with men (MSM). The past decades, infections were mainly confined to HIV-infected MSM. Although the advocacy and empowerment of these men in society and healthcare is well organized, they too are subject to stigmatization and struggle with mental and social problems [2]. It is assumed that in this group, high risk behaviour, partly driven by stimulant drug use, likely in combination with a biological susceptibility caused by HIV-infection and other sexually transmitted infections (STI), has led to sexual spread of HCV from probably the nineties onwards, with a major increase since 2000 [3, 4]. The development of this new epidemic has raised a need for studies investigating the incidence rate in this specific population and risk factors for transmission. Understanding high risk behaviour is essential for the development and implementation of tailored interventions aimed at reducing risk behaviour. In addition, optimization of treatment may be key in not only diminishing morbidity and mortality but also minimizing or eliminating this epidemic. Studies on HCV incidence, risk behaviour and treatment in HIV-infected MSM are part of this thesis.

5.1 Optimizing HIV and HCV treatment access and outcome in PWID

Globally, the burden of HCV-infection among PWID is high; in a systematic review it was estimated that in 2017, worldwide, 52% of PWID were HCV antibody positive [5]. In general, in 23% of all new HCV infections worldwide, injecting drug use was considered the route of transmission. Most new HCV infections among PWID are concentrated in Eastern Europe (23%) and Southeast Asia (26%), North-America (17%) and Latin-America (14%) [6].
In the last decade, the development of the highly effective directly-acting antivirals (DAA) has strengthened the hope that this epidemic can be halted. To reach the goal of the World Health Organization to reduce new infections by 80% by 2030 [7], when compared to 2015, treatment with DAA should be particularly upscaled among PWID [8]. Not only will this lead to less morbidity and mortality on an individual and population level, it may also, together with use of harm reduction programmes, have a major impact on the epidemic by decreasing transmission rates in regions with ongoing transmission [9-11]. Access to

treatment is limited though; a review of studies concerning several Eastern European and Asian countries, regions with the highest HCV prevalence among PWID, demonstrated that <1% of chronically infected PWID had been treated [12]. Treatment rates among PWID in high-income countries are slightly higher, for example <10% in Australia, but still remarkably low [13]. The expected negative influence of drug use on treatment adherence has been one of the main reasons for healthcare workers not to start treatment among PWID [14]. An association between non-adherence and drug use has been shown in several early studies focused on HIV treatment among PWID [15, 16]. Replacing or combining illicit opioid use with opioid substitution treatment (OST) may therefore improve adherence [17]. In Amsterdam OST is part of a broader low-threshold harm reduction programme, which also includes needle and syringe exchange, and medical and social care. This provides the opportunity of an individualized approach in which different intensities of harm reduction can be implemented. In **chapter 2.1** we demonstrated that HIV-infected PWID who receive harm reduction have excellent antiretroviral therapy (ART) adherence levels. Our data suggest that the extent to which a drug user receives structural social support, and not so much the intensity of harm reduction (i.e. using methadone or not, dosing of methadone, exchanging needles or not etc.), is important for the level of ART adherence. Overall, this study underlines the importance of structural social support and an integrated treatment approach for optimal ART treatment adherence among HIV-infected PWID. Similar results and conclusions are presented for HCV treatment adherence among PWID [18-22].

Although these results are positive, one should be aware that the drug policy in the Netherlands is quite exceptional and favourable with respect to infection risk. In a large part of the world, HCV treatment access remains limited for PWID as outlined above. Besides adherence issues, the fear of psychiatric complications and reinfection are reasons not to start HCV treatment in PWID. Many practice-based studies have proven the contrary though, demonstrating that effective HCV treatment is feasible in former or active drug users [23-25]. In **chapter 2.2** we describe how (pre-DAA) HCV treatment of PWID can be successfully achieved in a low-threshold, multidisciplinary setting, despite active drug or alcohol use. Treatment outcome was comparable to that in the non-PWID population. This integrated health care model has repeatedly proven to be effective for even more marginalized PWID populations [21]. Most guidelines therefore no longer state drug use as an exclusion criterion for treatment [24, 26, 27]. Since 2011 DAA have been available for patients with chronic HCV and proven to be very effective with few side-effects. Recently, several studies have demonstrated successful outcomes with DAA treatment among PWID [19, 28-30]. Furthermore, two studies, including a study using data from Amsterdam, have made it plausible that DAA treatment in the PWID population is highly cost-effective [31, 32]. Moreover, reported reinfection rates after successful treatment are low among PWID,

ranging from 1-5% per year (depending on rate of active drug use in the study population) in both pre-DAA era [33-35] and DAA era [36], therefore not offsetting cost-effectiveness [32]. In practice, the simultaneous use of DAA and OST does not lead to significant drug-to-drug-interactions or negative treatment outcome [37-39]. Some caution should be taken when combining DAA and anti-epileptics or short-acting benzodiazepines, often used by PWID suffering from mental illness [40].

Despite the evidence for the all-access integrated treatment strategy, stigma and drug policy still deprive a highly affected population of PWID in Eastern Europe, Russia, East and Southeast Asia and Northern America from appropriate care [41]. With restricted or no access to harm reduction the incidence of HIV and HCV infection remains high compared to other countries [42]. For example, the current prohibition of OST in Russia causes great concern due to the development of an HIV epidemic, in which prevention of further transmission is essential to decrease morbidity and mortality [43, 44].

Furthermore, in both low- and high-income countries the high pricing of DAA is a major obstacle to engagement in treatment as described in the last paragraph of this chapter. Overall, inequality in uptake remains for vulnerable and often marginalized patients with substance abuse and mental health disorders [45]. Efforts to optimize treatment for this specific population should continue.

Research and public health recommendations for HCV treatment in PWID

Most clinical studies on DAA have excluded people who were actively using drugs, some allowed inclusion of individuals using OST. Since in many countries the prevalence of HCV infection is particularly high among active drug users, it is recommended to perform more "real-world" studies on DAA treatment among this more challenging population [46]. Discussion exists whether upscaling of treatment or upscaling of harm reduction programmes is most effective in restraining the epidemic among PWID. Mathematical modelling demonstrated that upscaling of harm reduction strategies is cost-effective [47], and may have the most impact on restraining the epidemic in PWID [48]. Fraser et al. concluded that combination of treatment and harm reduction interventions, specifically OST and provision of sterilizing injecting equipment, is needed to reduce HCV infection to minimal levels [49]. A review of different modelling studies affirms that upscaling of treatment is required as well, and is in favour of upscaling a combination of both [50].

Different DAA treatment models should also be evaluated for cost-effectiveness [32]. For example, a model in which cost-effectiveness of PWID treatment at an addiction outpatient clinic in a liaison construction with hepatologists, is compared to that of treatment at the hepatology or infectiology outpatient ward in a hospital with support of an addiction specialist. Further expansion of treatment by specialized nurse-practitioners may facilitate the availability and reduce costs [51].

Another question is how harm reduction programmes and treatment facilities can be upscaled efficiently. This will not only depend on the epidemiological situation but also the political framework and availability of resources. Part of the debate regarding efficiency and cost-effectiveness of treatment is the question whether treatment should be prioritized to high-risk or low-risk groups. Treatment of high-risk persons may prevent more new infections, but this is also the group in which reinfections are more common. Modelling studies can attribute to answering this question [52], though translating results to clinical practice may be difficult.

Last but not least, an important aspect related to cost-effectiveness and treatment indication is the attained quality of life after effective treatment [53]. Improvement of quality of life after HCV clearance is not self-evident among PWID, who often suffer from co-morbidity (HIV infection, lung disease, addiction) and psychosocial problems. It will be useful for treatment programme development and decision-making to specify the most important factors that influence quality of life during and post treatment.

5.2 Mapping the HCV epidemic in MSM

Incidence of primary infection

Early recognition and monitoring of an occurring epidemic is essential for guiding and evaluating transmission prevention and disease control. The HCV epidemic among MSM in the Netherlands was first recognized in Rotterdam in 2003 [54]. The impact became clear in the longitudinal cohort-study among MSM in Amsterdam, published in 2007 [55]. In **chapter 3.1** we updated this study investigating the incidence of primary infection among MSM in the Amsterdam Cohort Studies (ACS) from 2003 to 2012. HCV incidence among HIV-infected MSM increased rapidly between 2000 and 2005 but seems to have stabilized thereafter at 12/1000 person years (PY). Both rise and stabilization correspond with results of prevalence studies among HIV-infected MSM at the STI outpatient clinic in Amsterdam [56, 57]. Internationally, the HCV incidence differs per region, but overall remains high, mainly affecting HIV-infected MSM. Data from the CASCADE Collaboration (Concerted Action on SeroConversion to AIDS and Death in Europe) used data from 16 cohorts in Europe, Australia and Canada and observed a continuous increase in incidence among HIV-infected from 1990 until 2014 [58]. Stratified by geographical region it turned out that HCV incidence declined after 2009 in Western Europe, increased in Northern Europe and remained stable in Southern Europe. Two meta-analyses confirmed the global upward trend of HCV incidence in this population; the meta-analysis of Hagan et al. of 17 HCV incidence studies with data up to 2012 among HIV-infected MSM found a pooled incidence rate of primary HCV infection of 5.3/1000 PY with an upward trend from 1991 (4.2/1000 PY) to

2012 (13.4/1000 PY). Furthermore, the pooled reinfection rate was twenty times higher [59]. In a meta-analysis of 28 studies among both HIV-uninfected and HIV-infected MSM, the pooled incidence was 6.3/1000 PY and 19 times higher among HIV-infected compared to HIV-uninfected MSM [60]. Hopefully, in the near future it will become evident whether upscaling of DAA implementation will confine these incidence rates, as has already been demonstrated in the Netherlands [61].

Until recently, the HCV epidemic almost exclusively affected HIV-infected MSM. A small number of cases of acute HCV infection and low incidence among HIV-uninfected MSM have been reported [60, 62, 63]. However, a screening of HIV-uninfected MSM participating in the Amsterdam PrEP (Pre-Exposure Prophylaxis) demonstration project (AMPREP) revealed that 4.8% were anti-HCV and/or HCV RNA positive at the beginning of the study and before starting PrEP [64]. This raised the concern that the HCV epidemic is now expanding irrespective of HIV status. The authors of this study emphasized that the results cannot be extrapolated to all HIV-uninfected MSM, since men who need PrEP almost by definition perform risky sexual behaviour. This was confirmed in a subsequent study among the larger population of HIV-uninfected MSM attending the STI clinic in Amsterdam, showing that anti-HCV prevalence was 1.0% in this population and remained stable over time [65]. The results do implicate that primary HCV prevention should also be focused on HIV-uninfected MSM engaged in HCV-associated risk behaviour. The finding has been confirmed by recent studies from France where incidence rates of acute infection were similar among HIV-infected MSM and HIV-uninfected MSM using PrEP [66]. Phylogenetic cluster analyses in the studies from the Netherlands and France showed that there is an overlap in sexual networks of HIV-infected and uninfected men.

Incidence of reinfection

In **chapter 3.2** we demonstrated a high incidence of reinfection of 15.2/100 PY among MSM previously treated for HCV infection. This has been one of the first studies worldwide providing evidence of HCV reinfection in the MSM population. It also made clear that relapse after treatment is actually often reinfection, which is important to acknowledge in relation to treatment guidance. The incidence of reinfection among HIV-infected MSM in a multicenter European cohort study between 2001 and 2014 was 7.3/100 PY [67]. Only a slight, non-significant decrease of reinfection incidence was apparent between 2010 and 2014. In a prospective cohort-study among Canadian MSM, the reinfection rates varied according to risk with highest rates in men who injected drugs and men with high risk sexual behaviour [36]. The incidence rates of reinfection in a German cohort were compared between the DAA era and interferon era, and there appeared to be no significant difference [68]. In the recent study among HIV-uninfected MSM starting PrEP in Amsterdam, the HCV reinfection rate during PrEP use was remarkably high at 25.5/100 PY [69]. To the best of our knowledge, there

are no studies that report a recent significant decrease in reinfection rates. Summarized, current trends suggest that prevention measures should continue, particularly focused on those at risk of reinfection and PrEP-users.
The long-term health effects of repeated infection and DAA treatment are not known yet and should be subject of future studies. Furthermore, frequent infections increase the chance of transmission of DAA-resistant variants, which may debilitate effective treatment [70]. Resistance guided treatment might offer a method to surpass the negative consequences of resistant strains on treatment outcome [71].

5.3 Optimizing treatment of acute HCV-infection in MSM

Since the availability of HCV-treatment, guidelines advice to wait for spontaneous clearance of acute infection and to only start treatment when infection is or has become chronic [72]. In HIV-infected individuals the rate of spontaneous clearance is 15.4% (pooled data), which is 10-20% lower than in HCV-monoinfected individuals [73]. In the pre-DAA era the success rates of chronic HCV infection treatment were much lower in HIV-coinfected than HCV-monoinfected individuals [74]. This, in combination with the low probability of spontaneous clearance, raised the question whether spontaneous clearance should be awaited in co-infected individuals. Several studies showed high Sustained Viral Response (SVR) rates among HIV-coinfected patients when starting peginterferon treatment early [75, 76]. Discussion also remained concerning optimal treatment duration. In **chapter 3.3** we retrospectively examined treatment outcome and the effect of treatment duration among HIV-infected MSM with acute HCV infection. In this study we demonstrated that treatment in the acute phase was very effective and that shorter treatment duration (24 weeks instead of 48 weeks) with peginterferon and ribavirin was sufficient. In the meantime, treatment with peginterferon has become obsolete and treatment of chronic HCV infection with DAA, even a very short course, has proven to be highly effective in both HCV-monoinfected and HIV-coinfected patients [77, 78]. The advice to await spontaneous clearance has therefore remained and DAA have not officially been approved for treatment of acute HCV infection [79]. Yet, on an individual and population level there may still be reasons to start DAA treatment as early as possible. First, on an individual level, the goal of treatment is reducing morbidity and chance of mortality. Several case reports and small studies have been published which validated the favourable treatment outcome of early treatment in HIV-infected MSM [80, 81]. Furthermore, some studies indicate that liver fibrosis evolves more rapidly in HIV-coinfected individuals and co-infection may in the acute phase even lead to fulminant liver failure [82-85]. Vogel et al. have opposed these results, arguing fibrogenesis does progress faster during the acute phase of HCV infection but progression rates are not

lineair and level off to rates found among HCV-monoinfected individuals [86]. This would imply that early treatment is not evidentially more advantageous for preventing liver fibrosis. These findings were confirmed in a cohort of 313 HIV-infected MSM with acute HCV infection, including MOSAIC participants. [87]. Studies with more sensitive tests and long-term follow-up are needed to clarify this issue. Second, on a population level, the reason for starting treatment prompt after diagnosis of acute infection is preventing ongoing transmission, as will be discussed further below in the paragraph '*Treatment as prevention*'.
A reason to delay treatment initiation may be the costs of upscaling DAA treatment. Popping et al. were the first to compare the influence of different DAA treatment scenarios on the epidemiology of HCV among MSM in the Netherlands and its cost-effectiveness in a mathematical model [88]. The authors concluded that early treatment of acute HCV is cost saving and also reduces the epidemic considerably. They also showed that a lower price is indeed favourable for cost-effectiveness. Furthermore, there was a strong impact of testing frequency, warranting frequent routine testing in clinical care. Despite cost-effectiveness of early treatment, DAA treatment costs do remain too high.

5.4 HCV risk factors, contexts and risk reduction among MSM

Sexual risk behaviour

Since the emergence of the HCV epidemic among MSM, it has become clear that in this population the virus is transmitted mainly during sexual contact. Combining the outcomes of various cohort and case-control studies from 2003 onwards leads to the conclusion that HIV infection, rough sexual techniques and ulcerative STI, which may cause damage of anal mucosal tissue, are strongly associated with HCV infection [89]. In addition, there is an association with sexualized drug use, which could be of either direct cause (transmission through sharing equipment when snorting or injecting) or indirect cause (stimulating prolonged sexual acts and lowering the barrier for more rough techniques). To motivate these men to implement risk reduction measures, it is obviously necessary to first of all provide them with accurate knowledge on possible risk factors and methods to reduce risk. In **chapter 4.1** the results are presented and discussed of a case-control study focusing on risk factors for HCV infection among HCV-infected and uninfected HIV-infected MSM from the MOSAIC study. In this study, we evaluated the role of sexual and drug use risk behaviour in detail, next to certain clinical characteristics. Receptive unprotected anal intercourse, sharing sex toys, unprotected fisting, injecting drugs, sharing straws when snorting, lower CD4 cell count and recent ulcerative STI were independently significantly associated with HCV infection. These results in part underlined previous and more recent findings [60, 90-92], although discussion remains on the significance and attribution of each factor.

HIV and STI

The biological vulnerability to HCV infection arises from different pathological mechanisms. The influence of pre-existing HIV infection on a biological level is still to be pinpointed. It is known that HIV causes depletion of CD4 T-cells in the gut mucosa which partly remains despite effective treatment with cART [93]. This deficient immunity in the gut may increase the efficiency of HCV transmission during anal sex. In addition, HIV infection leads to activated Langerhans cells which facilitate HCV transmission [94]. More studies into the role of HIV on the risk of HCV transmission are needed.

Furthermore, it is demonstrated that HCV RNA levels in serum are higher in HIV-infected compared with HIV-uninfected. This increases the risk of transmission within the network of HIV-infected MSM with HCV [95]. The chance of transmission increases when performing risky sex within the attained network of HIV-infected MSM where the chance of meeting a HCV-infected sex-partner is high [96]. In studies evaluating multiple potential risk factors, a history of recent or present STI is consistently associated with an increased risk of HCV infection [60]. In part this association may be explained by high risk sexual behaviour leading to both HCV infection and other STI. In our risk factor study, we found that after adjusting for high risk behaviour, infection with syphilis and/or lymfogranuloma venerum, both ulcerative diseases, remained associated with HCV infection. This finding suggests that these STI increase the vulnerability for infection by damaging the mucosal barrier, most likely in both HIV-infected and uninfected MSM.

Both prevalent or incident HIV-infection and other STI can be considered as markers for high risk behaviour and are prevalent in a high-risk sexual network of MSM. In such a network HIV serosorting (choosing sex partners with the same HIV serostatus) may have replaced condom use as a risk reduction strategy. On top of that, men may feel less compelled to use condoms now that there is strong evidence that a person with an undetectable HIV load cannot transmit HIV [97, 98]. The implementation of PrEP may have the similar effect. Recent results from two year follow-up of MSM starting PrEP in the Netherlands indicate that there was an increase in the number of condomless anal sex acts with casual partners, but STI incidence was stable, though high, specifically in the daily (versus event-driven) group [99]. The recent finding of spread of HCV among HIV-uninfected PrEP-users raises the question to what extent HIV infection actually attributes to the risk of becoming HCV infected, despite the above-mentioned possible mechanisms. It is likely that unprotected mucosa-damaging sex in a high risk (HCV-prevalent) network makes sexual transmission possible and biological vulnerability through HIV infection increases the chance of transmission even more.

Drug use

Drug use to facilitate sex, also called chemsex or sexualized drug use, is a major issue in this epidemic, and gaining more and more attention as a HCV risk factor [100-102]. In cross-

sectional studies from the United Kingdom prevalence of chemsex among (HIV-infected) MSM ranged from 17% [103] to 30% [104]. Comparable prevalence rates are reported from the Netherlands (up to 35%) [105, 106] and France (30%) [107]. A multi-site European study concluded that chemsex prevalence varied between study sites, discussing the influence of local and social norms [108].

Even though chemsex is considered to be recreative and to facilitate sex, other reasons to use drugs might be to decrease feelings of stress, anxiety and insecurity related to coming out, HIV diagnosis, suffering of depressions and experiencing marginalization and stigmatization [104, 109]. Interventions to influence problematic drug use should therefore be focused on both the personal struggles and the sexual and psychosocial context that urge men to use drugs.

Different types of drugs are used, but predominantly stimulants. Poppers have been popular in the gay scene for several decades. In more recent years crystal methamphetamine (also called crystal meth or Tina) is used by MSM with the purpose of increasing sexual drive, pleasure and endurance [100]. In the MOSAIC risk factor study (chapter 4.1) 61% of HCV-infected MSM used poppers nasally and at least 11% of HCV-infected men used crystal meth orally [110]. Ecstasy, gamma hydroxybutyric acid (GHB) and ketamine are other popular drugs used for sexual activity. In the MOSAIC study 70% of HCV-infected participants reported oral ecstasy use and 48% GHB use. These drugs have an euphoric, energizing effect and increase libido. Harmful effects on short term use are acute mental distress and the risk of overdose. GHB overdose may lead to unconsciousness and respiratory depression [100]. Mephedrone is another stimulant drug associated with sexualized drug use. In a survey on chemsex among MSM at routine STI screening or using an online dating app in the Netherlands, 20% of participants confirmed the use of this drug in the last 6 months [106]. The association of drug use with HCV infection in this population is twofold; to begin with, several studies indicate that injecting of drugs (slamming), specifically crystal meth, takes place among MSM [102, 110, 111]. Sharing of needles, which can lead to transmission of HCV, does not seem to happen often: e.g. among 2/12 (16.7%) of injecting MSM (of a total 213 participants) in the MOSAIC risk factor study [110]. Yet, the proportion injecting and sharing needles and/or syringes varies considerably across studies according to a recent systematic review, and should remain a point of concern [101]. A more frequently applied method is snorting, for example cocaine. Sharing snorting equipment, such as straws, happens often. In the MOSAIC study 48.8% (104/213) reported nasally administered drug use and of them 51% shared straws (53/104) [110]. There is contradictory evidence from studies among PWID regarding the risk of HCV transmission when sharing this snorting equipment [112, 113], but in the MOSAIC study it was significantly associated with HCV acquisition, also after adjusting for sexual behaviour.

Moreover, the use of stimulant drugs leads to disinhibition which might result in less implementation of risk reduction strategies, more enduring and rougher sex with multiple partners, which is associated with mucosal damage and HCV transmission [114]. Besides the possibility of physical side-effects of drugs, intoxication or overdose, its frequent use may lead to (worsening of) depression [115] or development of psychosis [116, 117].

Awareness and knowledge

The first step in HCV risk prevention is becoming aware of risk and gaining knowledge on transmission routes. In **chapter 4.2** we demonstrated that during an earlier period of this epidemic the awareness of HCV and knowledge of transmission routes among MSM was quite high (and higher among HIV-infected MSM than among uninfected MSM), but the knowledge on HCV infection complications was lacking. This may have influenced the perceived threat of HCV infection and have led to sustained risk behaviour. A more recent qualitative study from the United Kingdom explored the knowledge of MSM about STI and possible related threats. It appeared that men perceived HIV and HCV as most threatening, but more detailed knowledge was generally lacking [118]. In an Australian study overall HCV knowledge among MSM was good, but the knowledge on HIV as a risk factor, treatment availability and status were not as good [119]. In conclusion, there is room for improvement of education about HCV (and HIV). It is expected that complications like liver failure will be less and less part of the prospect after HCV diagnosis given the increasing uptake of DAA [120, 121]. This poses the question which focus prevention messages should have. Is it still effective to educate men about the long-term effects of HCV infection? Men should be aware that sometimes infections are diagnosed late, and irreversible complications (cirrhosis) may have already developed. Men with high risk behaviour should become aware that long-term health effects of reinfection and repeated DAA treatment are not yet known. Besides methods to prevent infection, knowledge on the risk of reinfection should at least be discussed with all persons at risk. It would be useful to repeat our study and assess the present knowledge of HCV transmission and specifically of reinfection risk among both HIV-uninfected and infected MSM.

Risk reduction strategies

The main HCV risk reduction strategies arising from the results of the risk factor study in chapter 4.1 in this thesis include: condom use during anal sex, gloves use during fisting, single time use of condoms or gloves when having sex with multiple partners or sequential sex acts, not sharing drug use equipment, not sharing sex toys and reducing drug use.
If HCV infection does occur, it is key to prevent reinfection after successful treatment. Often, this requires adaptation of sexual behaviour. Noteworthy is the much higher incidence of reinfection compared to primary infection [67], implying that it is very challenging to change

risk behaviour in the group of MSM previously infected with HCV. Whether MSM actually implement risk reduction strategies to prevent reinfection is a topic we studied in **chapter 4.3.** More specifically, we asked men about their motives and barriers to do so. Having insight into these motives and barriers is essential to improve primary prevention or strengthen secondary prevention strategies. Several motives to prevent reinfection were mentioned. The burden of HCV treatment (for all participants treatment existed of peginterferon and ribavirin) was emphasized particularly. With the introduction of DAA-regimens, with relatively short treatment duration, few side effects and a very high success rate [122], this may no longer be a motive. Indeed, study participants themselves expressed their concern that the motivation to prevent reinfection may decrease with the implementation of less burdensome DAA treatment. It is well studied that optimistic beliefs about cART were associated with an increase in sexual risk behaviour in some HIV-infected populations [123, 124], though a meta-analysis of 56 studies comparing persons on cART with persons off cART actually suggests the contrary [125]. A comparable situation could happen with the availability of DAA treatment. This should be considered when MSM are effectively treated, and risk behaviour should always remain a priority topic to discuss at HCV diagnosis and during and after HCV treatment.
A considerable barrier to risk reduction is the disinhibiting effect of drug use. In our study, some men were quite outspoken in their opinion that risky sex was (and was continued to be) performed due to the influence of drugs. Limiting drug use should therefore be a main point in HCV transmission prevention strategies.

5.5 Optimizing HCV prevention among MSM

After considering all of the findings regarding biological and behavioural risk factors, HCV awareness and knowledge among MSM and their motives and barriers to have safer sex, a number of recommendations can be made to optimize HCV prevention and related research.

Primary prevention

Increasing the use of risk reduction strategies

Direct prevention of HCV transmission is likely to be achieved when during sexual activity no blood- blood contact or sperm-blood contact takes place. Direct protection methods may be single use of condoms during anal sex or gloves during fisting. Achieving an increase in condom use may prove to be difficult now that prevention of HIV transmission may also be reached by attaining undetectable viral load or using PrEP. Not sharing injecting equipment, sex toys and lubricant jars is recommended since this can otherwise lead to spread of infected blood [126].

On a population level, men can be educated and motivated for safe sex through campaigns on MSM-related websites, brochures, at health departments or recreational venues. The website www.nomorec.nl, for education of MSM in the Netherlands about HCV transmission and prevention, is an example of how online education can be developed in cooperation with the MSM community [126]. This website was initiated by MCFree, a collaboration between all relevant stakeholders with the aim to reduce the incidence of HCV infections among MSM in Amsterdam [127].

On an individual level, each HIV-infected MSM or high-risk HIV-uninfected MSM should receive tailored information on HCV transmission and risk reduction when visiting the HIV outpatient clinic, STI clinic or general practitioner.

To better understand the factors that impede or stimulate change in risk behaviour over time, iterative qualitative research among men with continuing risk behaviour and reinfection should be performed. It would also be interesting to expand individual interviews to group interviews in which the dynamics of peer pressure and stigmatization may be more directly observed and addressed. In practice, motivational interviewing can be a useful method to explore the motives, intentions and the obstacles men experience when considering and implementing risk reduction [128]. Also it may be effectively implemented as part of counseling in a clinic [129], if not yet in place. In case of sustained risk behaviour, treatment with cognitive behavioural therapy may provide skills to reduce this. It may lead to insight into personal motives and barriers and harmful behavioural patterns. Skills as for example the setting of boundaries when pressured by peers or limiting drug use can be practiced. Components of this type of therapy, such as assertiveness training, can also be included in an online modular training. Considering the important role the internet and social media play in connecting MSM it is rational to use these technologies for future research on effective and new interventions [130]. Previous interventions based on online technologies and social networking such as use of websites, chat rooms and social media have proven to be effective in increasing HIV testing rates and reducing HIV risk behaviour (at least on a short term) in this population [131-133]. The effect of similar interventions should be studied among men at risk for HCV (re)infection. At the Public Health Service in Amsterdam a study is initiated in which the effect of a tailored online behavioural intervention on preventing HCV reinfection (intervention 1), is compared to expanding free home-based testing for HCV reinfection (intervention 2) and to the combination of both [134].

Focusing on mental health and drug use

Key in STI (and thus HCV) prevention in this population is attention for syndemics of mental health disease. The prevalence of mental health disorders, such as depressive disorder and anxiety disorder is higher in the MSM population compared to the general population [97, 98]. Moreover, both quantitative and qualitative studies among MSM confirm the relation

between mental health problems and sexual risk behaviour [99, 100]. As long as psychiatric comorbidity and psychosocial factors are not sufficiently addressed and treated, self-efficacy in risk reduction may be negatively affected. In part connected to these problems is the increased amount of drug use in sexually active MSM. As discussed in the *`Drug use´* paragraph above, for many persons substances may be primarily used recreationally for pleasant effects, yet for some it provides a way of coping with low self-esteem, early traumatic events, and associated depressive symptoms and anxiety [104]. This underlines the need of tackling mental health problems, preferably at a young age, before destructive coping mechanisms such as excessive drug use have become a habit. Furthermore, the use of drugs to perform high risk sexual acts touches on the topics of sexual desire, norms and social pressure; topics that each individual deals with, influenced by one's own history, mindset and health. These various factors make it complex to limit chemsex on an individual and group level. Still though, several approaches, in the form of stepped- or combined care, may help to diminish drug use in the sexual context or make it less harmful. First of all, awareness and knowledge are at the base of harm reduction. Through the internet, information can be made accessible for all and presented in a factual way without moralizing opinions. In the Netherlands the Trimbos institute provides up-to-date information on recreational drugs. The fact that use of crystal meth seems restricted to a relatively small group of the MSM population, might be the reason that there is no elaborate information about this drug on the Trimbos website [135]. Yet, the upcoming of crystal meth labs in the Netherlands could be a precursor of increasing use [136]. Mainline developed the website www.sexntina.nl, which does specifically focus on MSM chemsex using crystal meth [137] . Educational and motivational interviewing, cognitive behavioural therapy and support groups may empower both a persons' motivation to reduce drug use and abilities to do so. Pharmacological treatment for substance dependence is limited. For all interventions it is preferred to take place at a healthcare provider specialized in gay health. Interventions at a group level may exist of providing information on risks of drug use and harm reduction methods on gay websites and venues [138]. If detox does not succeed, or relapse occurs, practice of harm reduction methods should be encouraged. For example, in Amsterdam it is possible to order a toolbox online, containing harm reduction materials such as clean needles [126]. More quantitative and qualitative studies may give insight into the precise motives for sexualized drug use, and the extent in which drugs are used outside the sexual context.

Secondary prevention

The barriers mentioned in the qualitative study (chapter 4.3) and the high reinfection rate (chapter 3.2) imply that implementation or uptake of primary prevention measures has been limited or even lacking in certain subgroups. It also poses the question whether emphasizing primary prevention is useful or whether focus should shift to secondary prevention, such as more frequent screening of specific populations or upscaling treatment.

Testing

Diagnosing HCV infection as early as possible might lead to earlier risk reduction and earlier treatment and reduce onward transmission to others. Therefore, screening of HCV in high-risk populations with regular intervals and/or shortly after risk behaviour, and with sensitive tests, may be an important strategy in halting the epidemic. Considering the fact that acute HCV infection is associated with ulcerative STI, it is recommendable to link HCV screening to STI testing and vice versa. An observational study describes earlier detection of HCV infection among HIV-infected and HIV status-unknown MSM, when routine HCV antibody testing is added to routine STI testing at a sexual health clinic in Amsterdam, the Netherlands [139]. Recent infections and reinfections will not be detected with this protocol. Results from another modelling study by Popping et al. suggest that using a more sensitive test (PCR instead of antibody test) rather than increasing frequency of antibody testing decreases the incidence of HCV among MSM significantly [140]. In addition, HCV antigen testing could be a cheaper but equivalent alternative to HCV RNA testing [141], attaining a specificity of 100% (95% CI 82-100) [142]. Combining primary antibody tests with antigen and RNA tests following a specific testing algorithm may be most effective at a lower cost [108]. Providing self-sampling or self-testing sets may be another way to increase the HCV testing uptake [143, 144].

Considering the above, for future prevention strategies and research it is recommended that not only HCV screening of MSM at public health services and HIV outpatient clinics is promoted and standardized. Screening of MSM followed in study cohorts and surveys should be continued and linked to risk questionnaires to catch on to signals of changing risk behaviour. The risk of primary and reinfection among HIV-uninfected MSM eligible for or on PrEP underlines the need of monitoring the larger population of HIV-uninfected MSM. The screening results should be combined with phylogenetic analyses [145]. In this way researchers and health care professionals will notice changes in incidence and in networks in time to direct prevention measures such as described above.

Treatment as prevention

Related to the above is the concept of treatment as prevention. A growing number of modelling studies, in both PWID and MSM, demonstrate that scale up of DAA treatment will limit the epidemic [47, 49, 50, 146-151], though the size of impact depends on the percentage and timing of scale-up and the combination with risk reduction. In a study by Martin et al., focused on the MSM epidemic in the United Kingdom, modelling the most propitious scenario (100% DAA treatment uptake within one year after diagnosis and 20% uptake among those non-recently diagnosed, combined with 20% risk reduction), led to a relative decrease of active HCV prevalence of 78% in ten years' time [150]. Prevalence reduced 71% when no risk reduction was assumed and 55% when only recently diagnosed patients were treated and no risk reduction was modelled. A modelling study using Swiss HIV cohort data,

looked into the effect of a combination of risk counseling and early DAA-treatment (called intensive intervention) on HCV prevalence among HIV-infected MSM [147]. The best effect was reached by this intensive intervention combined with 50% risk reduction. Overall, early treatment initiation seems to impact prevalence the most: a subanalysis demonstrated that just starting treatment earlier (i.e. not waiting until F2 stage liverfibrosis has developed) will also lead to a lower prevalence while not using the intensive intervention. A recent study using data of MSM in Berlin concluded that to reach the 80% incidence reduction target stated by the WHO, it is necessary to increase DAA treatment coverage to 100% of newly diagnoses and at least 25% of previously diagnosed combined with at least 40% risk reduction, endorsing the study from the United Kingdom [151]. In conclusion, these studies not only confirm the potential effect of treatment scale up on overall HCV prevalence, but also emphasize the advantage of starting treatment early after diagnosis and, in particular the need to combine it with effective behavioural interventions. One could hypothesize that the high reinfection rate in this population would limit the effect of treatment scale up. However, Martin et al included the reinfection rate in their model and still found a positive effect of treatment scale up.
Real-life data from Australia and the Netherlands suggest that unrestricted treatment access can indeed lead to considerable increase in treatment uptake [152, 153] and a sharp decrease in HCV incidence among HIV-infected MSM [61]. Cohort data from France and Swiss are less optimistic and illustrate that treatment scale up does not necessarily decrease HCV incidence rates among MSM living with HIV [154, 155]. These findings indicate that continuation of the upscale of both treatment and risk reduction strategies is needed.

5.6 Changing perspectives

The arrival of DAA has undeniably changed the perspective of persons that suffer from HCV infection or are at increased risk of becoming infected. The persons described in this thesis belong to two distinct populations. This thesis is therefore not only about the need to change perspectives, but also the need to consider different perspectives when doing so. Several challenges are to be overcome to warrant new horizons for all affected individuals, no matter their background.

Increasing the accessibility to treatment is the greatest challenge for the community of PWID [156] and improving prevention is the main goal to be achieved for the MSM in the Netherlands. Improving prevention of primary infection and reinfection is important for MSM and PWID globally, in particular in countries with stable or increasing HCV epidemics. This can only be achieved when taking into account a divergent range of contexts, lifestyles, beliefs,

expectations and hopes. Yet, the underlying forces that are to be turned are similar for both populations: stigmatization, rejection and exclusion of society, and syndemics of mental health and social difficulties. In the Netherlands the position of both risk populations is fairly strong. From the nineteen-seventies and onwards, emancipation of MSM and recognition of the need of support of PWID through low-threshold harm reduction programmes have led to good access to preventive and curative medical care. This fact, together with the longstanding scientific research that substantiates the Dutch policy, legitimizes and compels the Netherlands to take a leading role in the international action against the HCV epidemic and its underlying social and political roots.
Part of this role may be the continuous support of local programmes claiming equal rights and destigmatization. Another important part is to actively indicate ethical responsibility of pharmaceutical industries in providing DAA-access for all, by lowering its costs. In the last decade the access to HIV treatment increased immensely by lowering prices through the permission of generic manufacturing and competition [157]. A voluntary license agreement by Gilead with Indian manufacturers in 2015 has led to locally low priced generic DAA [158]. Generic manufacturers in other countries followed, leading to competition and steep price reductions [159]. Criticism concerns the fact that high prices remain in middle and high income countries and unrestricted generic competition is more effective and fair [160].

International policy is the playground of politicians, activists and policymakers. Yet, the input of researchers remains undeniably essential. Long-term cohort-studies are necessary to study in detail the dynamics of the epidemic that is shaped by human behaviour and (biomedical) interventions. Fundamental studies are needed to provide and test new insights in the biological basis of HCV transmission, disease development and elimination. Despite the existing barriers, the search for a preventive vaccine should continue. Clinical studies should be extended to real-world populations to tackle obstacles in treatment uptake and outcome and to find optimal ways of service delivery. It is evident that research should be increasingly performed in international cooperation; this is inherent to the nature of globally spread disease and indispensable to perform quality studies within confined funding.
Reaching (micro-)elimination is only possible when clinicians, epidemiologists, biomedical and behavioural researchers, prevention professionals, politicians, NGOs, activists, key populations and patients closely work together in controlling the HCV epidemic. The MCFree project in Amsterdam is an inspiring initiative and example of this kind of efficient partnership. In practice, the focus should be on both prevention and treatment, since the combination of both is considered most effective. Most of all, every professional involved should be truly and continuously aware of the needs of PWID or MSM. Constant involvement of and cooperation with these communities is key in creating change.

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Appendices

Summary

Changing perspectives
Hepatitis C virus infection in key populations

This thesis focuses on hepatitis C virus (HCV) infection in two key populations in the Netherlands: people who inject drugs (PWID) and HIV-infected men who have sex with men (MSM). It comprises five chapters, describing eight studies that were conducted to improve the prevention and disease management of HCV infection in these populations.

Chapter 1 provides an introduction into different aspects of HCV infection and the HCV epidemics among PWID and MSM in the Netherlands and globally. The aims and outlines of the different studies in this thesis are described and substantiated. HCV is a bloodborne virus that can lead to liver disease and is known to be predominantly transmitted through unhygienic medical procedures, sharing of injecting drug use equipment, and among HIV-infected MSM through sexual contact. Worldwide the HCV epidemic constitutes a major public health burden. The development of direct-acting antivirals, an efficient and effective new therapy, has changed the perspective for many chronically and newly infected persons. In the Netherlands, increasing HCV treatment uptake is the main challenge among HCV-infected PWID, and prevention of HCV (re)infection is the main concern among HIV-infected MSM.

In **chapter 2** factors are studied that are associated with adherence to HIV-treatment and success of HCV treatment in (former) PWID in Amsterdam, with the aim to optimize HIV and HCV care for this population. In PWID, illegal substance use (heroin, cocaine) might influence HIV-treatment adherence. Opioid substitution treatment with methadone (OST), a harm reduction method, has shown to improve HIV treatment adherence. In Amsterdam OST is part of a broader harm reduction programme that also includes needle and syringe exchange. In **chapter 2.1** we demonstrated that PWID who are exposed to systematic and integrated care, although not practising complete harm reduction, can be just as adherent to HIV-treatment as those who make use of complete harm reduction and people who do use drugs but do not inject (anymore). We therefore concluded that being part of a systematic and comprehensive support system is important for HIV treatment adherence among PWID. Alike HIV treatment, for years it was expected that HCV treatment was too complex and demanding to implement in the PWID population. The long duration of treatment with peg-interferon and ribavirin, the need for adherence, probable side-effects, high costs, the frequent prevalence of psychiatric co-morbidty and the prospect of possible reinfection, withheld physicians from starting treatment in this population. In **chapter**

2.2 the development, implementation and results of the multidisciplinary HCV treatment programme for HCV-infected people who use drugs (DUTCH-C) in Amsterdam is described. By offering low threshold HCV testing and treatment at the public health service instead of the hospital it was possible to test and treat drug users with chronic HCV infection successfully, despite active drug or alcohol use and psychiatric diseases. Therefore, access to HCV therapy using an integrated approach should be increased for this population.

In **chapter 3** we present studies on the epidemiology of HCV infection among HIV-infected MSM. Since 2000 an unexpected increase was seen in the number of acute HCV infection among HIV-infected MSM in high-income countries. Several studies demonstrated the increase was substantial, limited to HIV-infected MSM and not related to injecting drug use. Monitoring an epidemic is essential for timely and tailored interventions. In **chapter 3.1** we therefore estimated the incidence of acute HCV infection among HIV-infected and HIV-uninfected MSM participating in the Amsterdam Cohort Studies (ACS) between 1984 and 2012. All observed incident HCV infections were found in MSM who were HIV-infected. The overall HCV incidence was 4.52/100 person-years and a significant increase was observed after 2000. After 2005 the incidence stabilized, possibly due to increased awareness, reduced risk behaviour, and increased uptake of HCV testing and treatment.
Despite previous clearance it is possible to be reinfected with HCV when risk behaviour is continued. Even when the incidence of primary infection levels off, the disease burden can remain high in a subpopulation due to reinfections. In **chapter 3.2** the incidence of HCV reinfection among HIV-infected MSM from two outpatient clinics in Amsterdam was estimated 15.2/100 person years. This remarkably high incidence implied that in this specific population both new interventions to reduce risk behaviour, and more frequent and sensitive HCV testing are necessary.
On a population level the incidence can also be reduced by increasing the uptake of treatment and the percentage of successful treatment outcomes. In the pre-DAA era, treatment with peg-interferon and ribavirin could be effective, also in coinfected patients. It was stated that long treatment duration (48 weeks or longer) was needed for these patients, whereas a duration of 24 weeks was sufficient for HCV mono-infected patients. However, the longer duration was burdensome due to the frequent side-effects. In **chapter 3.3** we evaluated HCV-treatment with peg-interferon and ribavirin among HIV-coinfected MSM with an acute HCV infection and specifically the effect of treatment duration on outcome. We found that there was no statistically significant difference in outcome between HIV-infected MSM with an acute HCV infection treated for 24 weeks and those treated for 48 weeks, suggesting that shorter treatment duration may be sufficient for acute infection in coinfected patients. To prevent further spread of HCV among MSM and considering the high reinfection rate, it is essential to understand which risk behaviour leads to HCV transmission in this population.

Chapter 4 focuses on HCV risk behaviour, awareness and knowledge among HIV-infected MSM. In **chapter 4.1** the results are presented of a case-control study on risk factors for HCV infection in MSM participating in the MSM Observational Study of Acute Infection with hepatitis C (MOSAIC study). Questionnaires on risk behaviour were compared between HCV-HIV-infected MSM and HIV-infected MSM. Receptive unprotected intercourse, sharing sex toys, unprotected fisting, injecting drugs, sharing straws when snorting drugs, lower CD4 cell count, and recent diagnosis of ulcerative sexually transmitted infection were significantly associated with acquiring HCV infection in multivariate analyses.
In the study presented in **chapter 4.2** levels of awareness and knowledge of HCV infection were measured among HIV-infected and uninfected MSM participating in the ACS. Most men were aware of the existence of HCV infection and its transmission routes. Compared with knowledge of transmission routes, knowledge of disease complications appeared to be limited.
To further understand the impact of HCV infection on sexual risk behaviour, HIV-coinfected MSM, treated with peg-interferon and ribavirin, were interviewed on their ideas, motives and barriers concerning HCV risk reduction. **Chapter 4.3** presents the most important findings and interpretation of this qualitative study. Avoiding (pre-DAA) HCV treatment and its side-effects was the strongest motive to implement risk reduction strategies after clearance of previous infection. With the existence of the less burdensome DAA treatment this motive may disappear; a concern expressed by participants themselves. Barriers to safer sex were the sexual social norms, peer pressure, stigma and drug use during sex. Reducing drug use, strengthening disclosure skills and discussing sexual norms may therefore improve the self-efficacy for risk reduction among these men.

In **Chapter 5** we discuss the most important findings of the studies in relation to recent literature, and give suggestions for future research and prevention measures, taking into account the changing perspectives since the implementation of DAA treatment.
It has become clear that in the Netherlands the prevention and care regarding infectious diseases for PWID is quite favourable. It demonstrates that effective HCV care in this population is feasible and sets an example for countries where, due to socio-economic and political influences, the HCV epidemic in this population is rather increasing than decreasing. More 'real-world' research and strengthening of human rights in these settings are necessary to turn the tide for this vulnerable population.
The introduction of DAA has led to treatment of many HCV-infected MSM; yet, both primary infections and reinfections still occur among MSM with risk behaviour. Furthermore, with the recent spread of HCV among HIV-negative MSM eligible for or using PrEP, it is essential that education about primary preventive measures continues and effective methods to reduce risk are developed and implemented. The self-efficacy of MSM in implementing risk reduction

may be improved by a more specific focus on mental health and the impact of chemsex. In addition, secondary prevention may also play an important role in limiting the epidemic; optimizing testing policy may lead to earlier diagnosis of infection and subsequently earlier risk reduction and HCV treatment, reducing onward transmission to others. An increasing number of modelling studies demonstrate that the combination of upscaling of treatment and effective behavioural interventions is most effective in reducing the number of prevalent and incident infections.

Finally, to let the changing perspectives become a reality for all HCV-infected persons worldwide, it is essential to lower DAA costs and to improve and sustain international cooperation between all involved stakeholders, including key populations.

Samenvatting voor niet-ingewijden

Verandering van perspectieven
Hepatitis C virus infectie in risicogroepen

Het hepatitis C virus (HCV) is een virus dat na infectie in de levercellen nestelt en daar jarenlang aanwezig kan zijn zonder dat de geïnfecteerde persoon er klachten van heeft. Een chronische infectie kan na tientallen jaren leiden tot leverziekten, waaronder leverkanker, waardoor dit virus ook wel een sluipmoordenaar wordt genoemd. Er bestaan diagnostische testen en sinds de jaren tachtig ook behandeling voor HCV infectie. Vele mensen die HCV hebben zijn zich echter niet bewust van het feit dat zij geïnfecteerd zijn en zijn nooit behandeld. Op dit moment is de schatting dat er wereldwijd ongeveer 71 miljoen mensen chronisch geïnfecteerd zijn. Het is dus een buitengewoon mondiaal gezondheidsprobleem. Met de recente komst van een simpelere en effectievere behandeling is er nu de verwachting dat het toekomstperspectief van personen met HCV sterk verbeterd is. De World Health Organization (WHO) streeft ernaar dat in 2030 de incidentie (het aantal nieuwe infecties per 100 personen per jaar) van HCV met 80% is gereduceerd.

HCV is een virus dat via bloed-bloed contact wordt overgedragen. Er bestaan verschillende subtypes (genotypes). Het grootste risico op HCV infectie bestaat bij het verkrijgen van geïnfecteerd bloed tijdens een bloedtransfusie, een behandeling met geïnfecteerd chirurgisch gereedschap of naalden, en het delen van geïnfecteerde naalden of spuiten tijdens drugsgebruik. Transmissie van HCV via medische ingrepen is in de meeste westerse landen zo goed als uitgesloten doordat bloed gescreend kan worden op HCV en gereedschap gesteriliseerd. Het voorkomen van transmissie bij injecteren van drugs is mogelijk door het gebruik van schone naalden en spuiten. Dit wordt in Nederland gestimuleerd door gratis verstrekking van schone naalden en spuiten en vertrekking van methadon, waardoor de behoefte om heroine te spuiten afneemt. In veel niet-westerse landen is de preventieve HCV zorg voor druggebruikers nog steeds beperkt vanwege stigmatisatie van deze groep.

De kans op HCV transmissie tijdens heteroseksueel contact is zeer klein. Echter, onder hiv-geïnfecteerde mannen die seks hebben met mannen (MSM) is sinds de jaren negentig een onverwachtse stijging in aantal acute HCV infecties ontstaan, die samenhangt met seksueel risicogedrag in combinatie met een biologische kwetsbaarheid door het hebben van hiv en co-morbiditeit met bepaalde seksueel overdraagbare aandoeningen (SOA).

Er is 25% kans op het spontaan kwijtraken (klaren) van het virus na infectie. De meeste personen met HCV genezen dus niet zonder behandeling. In de jaren negentig zijn er

medicijnen ontwikkeld, (peg-)interferon en ribavirine, die, afhankelijk van het type HCV virus, redelijk tot goed effect hebben. Deze medicijnen gaven wel veel bijwerkingen. In de afgelopen vijftien jaar zijn nieuwe medicijnen, direct-acting antivirals (DAA), op de markt gekomen die zeer effectief zijn, minder lang genomen hoeven te worden en nauwelijks bijwerkingen hebben. De optimalisering van deze DAA voor alle HCV virus types is nog in volle gang. De resultaten zijn veelbelovend. Ook personen die naast HCV ook hiv hebben, kunnen effectief behandeld worden. Daarbij moet wel rekening gehouden worden met eventuele interacties tussen de hiv- en HCV-medicatie.

Het is bij continueren van risicogedrag mogelijk om na klaren of succesvolle behandeling opnieuw geïnfecteerd te raken met HCV (herinfectie). Er zijn aanwijzingen dat er in mensen een immuunrespons wordt opgebouwd tegen HCV, maar die is niet afdoende om te beschermen tegen herinfectie.

In dit proefschrift worden acht studies besproken, betreffende HCV infectie in twee risicogroepen in Nederland: (voormalig) injecterend druggebruikers met en zonder hiv, en mannen die seks hebben met mannen met hiv. Het omvat vijf hoofdstukken waarin de onderwerpen epidemiologie, risicofactoren en behandeling van HCV in deze twee groepen aan de orde komen.

Hoofdstuk 1 geeft achtergrondinformatie over het hepatitis C virus, de epidemiologie, transmissie-routes en behandeling, zoals hierboven samengevat. Tevens worden de verschillende doelstellingen van de acht studies benoemd en onderbouwd.

In **hoofdstuk 2** worden twee studies beschreven die als doel hebben bij te dragen aan het verbeteren van de zorg voor (voormalig) druggebruikers met hiv en/of HCV.
Het gebruik van drugs, zoals heroïne of cocaïne, kan invloed hebben op therapietrouw. Dat wil zeggen dat tijdens het gebruik van drugs mensen mogelijk eerder hun hiv- of HCV-medicatie vergeten of verkeerd innemen. Eerdere studies hebben aangetoond dat de therapietrouw bij mensen die drugs gebruiken toeneemt, wanneer zij stoppen of minderen met drugsgebruik door het toepassen van opioïd-substitietherapie. In plaats van heroïne (een illegaal opioïd) kunnen zij dan op voorschrift methadon (een farmaceutisch opioïd) gebruiken, hetgeen craving (extreem verlangen) naar heroïne voorkomt en gereguleerd en veilig is. In Amsterdam is gebruik van methadon onderdeel van een uitgebreider programma van "harm reduction" (methodes om drugsgebruik veiliger te maken). Een voorbeeld daarvan is de mogelijkheid om gratis schone naalden te krijgen voor degenen die nog wel injecteren en het verstrekken van methadon. In **hoofdstuk 2.1** onderzoeken we of er een verschil is in therapietrouw aan HIV medicatie tussen HIV-geïnfecteerde mensen die drugs gebruiken die

in verschillende mate harm reduction methodes gebruiken (wel of niet injecteren, wel of niet naalden omruilen, wel of niet methadon gebruik, dosering methadon gebruik). We hadden verwacht dat hoe meer methodes iemand gebruikte, des te beter de therapietrouw zou zijn. Dit bleek niet zo te zijn. Personen die namelijk nog wel drugs injecteerden, waren gemiddeld net zo therapietrouw als personen die niet injecteerden. Verder bleek dat personen die onder toezicht woonden en een partner hadden meer therapietrouw waren dan personen die niet deel waren van een dergelijke sociale structuur. Onze conclusie is dat ook wanneer iemand nog injecteert hij of zij therapietrouw kan zijn en dat het heel belangrijk is dat druggebruikers gebruik (kunnen) maken van sociale support omdat dat helpt therapietrouw te zijn.
Lange tijd werd gedacht dat HCV behandeling niet haalbaar was bij druggebruikers, omdat de behandeling langdurig was, met veel bijwerkingen, waarbij het noodzakelijk was zeer therapietrouw te zijn. Daarnaast werd verwacht dat druggebruikers die bleven injecteren groot risico hadden na behandeling opnieuw geïnfecteerd te raken. Het gevolg was dat decennia-lang een zeer hoog percentage van de (voormalig) injecterende drugsgebruikers een chronische HCV infectie had en niet behandeld werd. In **hoofdstuk 2.2** beschrijven we de opzet, implementatie en resultaten van de DUTCH-C studie (Drug Users Treatment of Chronic Hepatitis-C). Dit is een HCV-behandelprogramma specifiek voor druggebruikers in Amsterdam, dat werd uitgevoerd tussen 2009 en 2013. Door het bieden van een laagdrempelige test-service op de locatie van het al jaren lopende, en onder druggebruikers bekende, druggebruikers cohort bij de GGD Amsterdam, was het mogelijk om 449/497 (90%) druggebruikers te testen op HCV. Het bleek dat 60% van hen positief was voor antistoffen tegen HCV en 69% van deze groep bleek een chronische infectie te hebben. Vervolgens werd op dezelfde locatie door een arts en verpleegkundigen HCV behandeling aangeboden, in samenwerking met specialisten van het Academisch Medisch Centrum en medewerkers van de geïntegreerde voorziening van GGD Amsterdam die o.a. methadon verstrekt. Uiteindelijk zijn 58 personen met een chronische HCV infectie behandeld in de eerste vier jaar van het project, van wie 65% succesvol. De conclusie van de beschrijvende studie is dat bij gebruik van een multidisciplinair team op een laagdrempelige locatie buiten het ziekenhuis, het mogelijk is om druggebruikers met chronische HCV-infectie te testen en succesvol te behandelen, ondanks het bestaan van actief drugsgebruik en psychiatrische comorbiditeit.

In **hoofdstuk 3** gaan we in op de incidentie van acute HCV infectie en HCV herinfectie bij MSM met hiv, en de HCV behandeling in deze groep. Uit verschillende studies in onder andere het Verenigd Koninkrijk, Nederland, Frankrijk, Duitsland en de Verenigde Staten bleek rond het jaar 2000 dat er een opvallend hoge HCV incidentie onder MSM met hiv was, en er geen overlap was met mensen die drugs injecteerden. Om het ontstaan van deze nieuwe epidemie te begrijpen en een halt toe te roepen was het belangrijk veranderingen

in de incidentie goed te volgen en zo nodig op te reageren met het ontwikkelen van nieuwe interventies. In **hoofdstuk 3.1** maakten we doormiddel van het testen van opgeslagen bloedmonsters een schatting van de incidentie van acute HCV infectie tussen 1984 en 2012 onder MSM deelnemers van de Amsterdamse Cohort Studies (ACS) met en zonder hiv. Er werden alleen nieuwe HCV infecties gevonden bij deelnemers met hiv. De incidentie werd geschat op 4.5 per 100 personen per jaar. Er was een significante stijging in incidentie vanaf het jaar 2000 ten opzichte van de periode daarvoor. De incidentie stabiliseerde vanaf het jaar 2005, mogelijk door toegenomen bewustzijn van het risico op HCV, het verminderen van risicogedrag, en de toename in het testen op HCV en de behandeling.
Zelfs wanneer de incidentie van een eerste infectie in een groep stabiliseert of daalt, kan door het voorkomen van herinfectie de incidentie voor een subpopulatie met veel risicogedrag hoog blijven. **Hoofdstuk 3.2** toont een HCV herinfectie incidentie van 15.2 per 100 personen per jaar onder MSM met hiv in zorg op twee hiv-poli's in Amsterdam tussen 2003 en 2011. Deze opvallend hoge incidentie impliceert dat er in deze specifieke populatie noodzaak is voor zowel nieuwe preventie interventiemethodes om het risicogedrag te verlagen, als een optimalisering in frequentie en gevoeligheid van HCV testen.
Op populatie niveau kan de epidemie beperkt worden door het percentage succesvol behandelden te verhogen. Voordat de huidige antivirale therapieën bestonden (DAA) kon behandeling met peg-interferon en ribavirine ook bij personen met zowel een HCV als hiv infectie succesvol zijn. Er werd lange tijd gedacht dat het daarvoor wel noodzakelijk was om deze groep langdurig te behandelen (48 weken of langer). Dit kon moeizaam verlopen door de frequente en vervelende bijwerkingen. In **hoofdstuk 3.3** evalueerden we de uitkomst van HCV-behandeling met peginterferon en ribavirine bij 50 HCV-HIV geinfecteerde MSM met hiv en HCV, en in het bijzonder het effect van de duur van behandeling op de uitkomst. Het bleek dat er geen significant verschil in uitkomst was tussen de personen die kortdurend (24 weken) of langdurend (48 weken) behandeld werden. Dit suggereert dat een kortere HCV behandeling ook toereikend is voor de mensen met hiv en acute HCV.

Om effectieve HCV preventie-adviezen te kunnen ontwikkelen is het essentieel om inzicht te verkrijgen in de risicofactoren voor HCV transmissie in de MSM populatie. **Hoofdstuk 4** focust op HCV risico gedrag, bewustzijn en kennis onder MSM met en zonder hiv. In **hoofdstuk 4.1** worden de resultaten gepresenteerd van een case-controle studie naar de risico-factoren voor HCV infectie bij MSM, participerend in de MOSAIC studie (MSM Observational Study of Acute Infection with hepatitis C). Vragenlijsten over risicogedrag van 82 MSM met hiv en HCV (de cases) werden vergeleken met die van 131 MSM met alleen hiv (controles). Receptieve onbeschermde anale seks, delen van seksspeeltjes, onbeschermd fisten, injecteren van drugs, delen van rietjes tijdens snuiven van drugs, een lager CD4-

aantal, en recente diagnose van een ulceratieve soa waren allen onafhankelijk van elkaar significant geassocieerd met het oplopen van een HCV infectie.
Hoofdstuk 4.2 beschrijft een studie waarin de mate van bewustzijn van en kennis over HCV gemeten werd bij MSM met en zonder hiv die deelnemen in de ACS. De meeste mannen bleken zich bewust te zijn van het bestaan van HCV infectie en ook de bekendste transmissieroutes. Zij waren veel minder bekend met de mogelijke lange termijn effecten van chronische HCV infectie op de gezondheid.
De laatste studie, **hoofdstuk 4.3**, exploreert op kwalitatieve wijze de invloed van HCV infectie op het risicogedrag van mannen, om aanknopingspunten te vinden voor het ontwikkelen van methodes gericht op preventie van herinfectie. Voor deze studie werden 20 hiv-geïnfecteerde mannen die HCV behandeling (hadden) ondergaan met peg-interferon en ribavirine, geïnterviewd over hun ideeën, motivaties en barrières betreffende het toepassen van HCV risico-reductie. De belangrijkste motivatie die werd beschreven om veiliger seks te hebben was het willen vermijden van opnieuw ondergaan van HCV behandeling (zoals ervaren voordat er DAA waren), vanwege de vervelende bijwerkingen. Nu er behandeling bestaat die minder belastend is zou deze belangrijkste motivatie kunnen verdwijnen. Barrières om veiliger seks te hebben die werden genoemd door de deelnemers: de heersende seksuele normen in deze subpopulatie, de bestaande verwachtingen en druk vanuit de groep, stigma ten aanzien van het hebben van HCV en de invloed van drugsgebruik gedurende seks (chemsex). De verwachting is dat risico-reductie vaker kan worden toegepast wanneer mannen het drugsgebruik verminderen, het stigma afneemt en mannen zich zekerder kunnen voelen in het bespreken van de HCV diagnose en risico-reducties methodes met hun seksuele partners. Openheid en delen van informatie vanuit de gemeenschap zelf is één van de manieren om dit te bewerkstellingen.

De belangrijkste bevindingen van bovenstaande studies worden in **hoofdstuk 5** (de discussie), besproken in het kader van relevante en recente literatuur. Daarbij worden, vanuit het besef dat DAA behandeling het perspectief voor mensen met HCV heeft veranderd, voor beide risicogroepen aanbevelingen gegeven voor toekomstig wetenschappelijk onderzoek en preventiebeleid.
Voor personen met HCV of risico op HCV door (voormalig) injecteren van drugs is de preventieve en curatieve zorg in Nederland gunstig. In landen met sociaaleconomische uitdagingen, waar vanuit politiek en samenleving vaak drugsgebruik gestigmatiseerd en soms ook gecriminaliseerd wordt, is dat niet zo en blijft de prevalentie en incidentie van HCV in deze populatie vaak hoog. Onderzoek in deze setting en populatie, en het bevorderen van gelijke mensenrechten in deze landen, kan bijdragen aan verbetering van de gezondheid van deze groep.

Introductie van DAA heeft geleid tot behandeling van veel MSM, maar primaire infecties en herinfecties blijven wel nog voorkomen en naar nu blijkt ook bij MSM zonder hiv, die wel door onveilig seksueel gedrag risico lopen op een hiv infectie. Dit pleit voor het blijven investeren in voorlichting en vinden van manieren om risico op transmissie te reduceren. Aandacht moet daarbij vooral ook uitgaan naar het versterken van het vertrouwen in eigen kunnen ('self-efficacy') van mannen in het toepassen van risico-reductie. Het optimaliseren van de geestelijke gezondheid en het toepassen van behandeling voor en 'harm reduction' van drugsgebruik rondom seks zullen hierin een rol moeten spelen. Daarnaast is een optimaal testbeleid en uitbreiden van het aantal behandelden een onderdeel van preventie. Het is daarvoor wenselijk dat de huidige hoge kosten van DAA wereldwijd verlaagd worden.
Concluderend zal voor het behalen van het mondiale WHO doel om de HCV incidentie per 2030 met 80% te verlagen, het uitbreiden van de combinatie van preventie en behandeling, alsook interdisciplinaire samenwerking in zorg, onderzoek en beleid met inbreng van de doelgroepen, voorop moeten staan.

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Chapter 2.2
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Chapter 3.1
Stabilizing incidence of hepatitis C virus infection among men who have sex with men in Amsterdam

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Chapter 4.1
Risk factors for sexual transmission of hepatitis C virus among human immunodeficiency virus-infected men who have sex with men: a case-control study

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Chapter 4.2
High awareness of hepatitis C virus (HCV) but limited knowledge of HCV complications among HIV-positive and HIV-negative men who have sex with men

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Chapter 4.3
Changing the odds: motives for and barriers to reducing HCV-related sexual risk behaviour among HIV-infected MSM previously infected with HCV

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