Hepatitis C virus infection: Spread and impact in the Netherlands
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CHAPTER 1
GENERAL INTRODUCTION
Hepatitis C Virus

Hepatitis C virus (HCV) was identified in 1989 and was recognized as the causative agent of post transfusion non-A, non-B hepatitis (1). HCV is single stranded RNA and primarily a blood-borne virus which causes persistent viremia in 75% of those infected (2). Over decades, chronic infection can lead to progressive liver disease such as liver cirrhosis or liver carcinoma (3). HCV is less infectious than HBV; when having a needle stick accident, the risk for HCV transmission is 3% compared to 30% for HBV and 0.3% for HIV (3). The introduction of HCV testing in 1991, in addition to the screening of donor blood, significantly decreased the risk for blood transfusion- and blood products -associated HCV infection (3).

Epidemiology

Worldwide about 130–170 million people are chronically infected with the hepatitis C virus, which makes HCV the leading cause of chronic liver disease (4). It is estimated that 3–4 million people are infected with HCV each year (5) and more than 350 000 people die from hepatitis C-related liver diseases each year (5).

In high endemic countries, new HCV infections are often health-care associated, i.e. transmission can take place by re-using medical equipment. In addition, transmission occurs through injecting drug use, for example in high endemic countries in eastern Europe (6). Other activities involving poor hygienic conditions can also cause blood-to-blood contact such as cultural/religious practices and barber shop shaving. Household contact with a chronic carrier is considered a risk as well; HCV can be transmitted by, for instance, sharing e.g. razors or dental material. Countries with high rates of chronic infection are Egypt (22%), Pakistan (4.8%) and China (3.2%) (5). Egypt has the highest HCV prevalence due to a mass parenteral treatment campaign against schistosomiasis which took place from 1920 to 1980 in which the injection materials were not sufficiently sterilized (7).

In contrast, the majority of new HCV infections in low endemic countries where HCV transmission was effectively halted by the introduction of donor blood screening in 1991 occur within specific risk groups (4;8). The largest risk group in low endemic counties are injecting drug users (IDU) with the prevalence of infection ranging from 60-80% (9).
Mother-to-child transmission occurs in 4-7% of RNA-infected mothers, this rate increases to 19% when the mother is HIV-positive (11). HCV is not known as an STI and rarely transmitted through sexual intercourse, even in the presence of HIV co-infection (12). However, recent outbreaks of acute HCV among HIV-positive men who have sex with men (MSM) who deny IDU have been observed. Longitudinal cohort studies have confirmed a marked increase in HCV incidence among HIV-positive MSM, but not HIV-negative MSM, after the year 2000. In the Amsterdam Cohort Study, HCV incidence rose 10-fold to 8.7 per 1,000 person years in the period 2000-2003 compared with 0.8 per 1,000 person years in the period 1984-1999 (13). Thereafter HCV prevalence continued to increase in Amsterdam, as described in chapter 3.1.2 and 3.1.3. An increase in prevalence and/or incidence has been observed in other countries as well (14;15).

Clinical course of HCV infection

Clinical course

HCV is mainly an asymptomatic disease, and in its acute phase only 20% of cases experience aspecific flulike symptoms like nausea, fever, abdominal pain and occasionally jaundice (16). Clinical manifestation can occur within 7-8 weeks after exposure to HCV. Because of its asymptomatic course, HCV is usually discovered in a late stage of the disease. Natural clearance of the virus occurs in about 25% (2) of the patients, and has been associated with female sex, younger age at infection, being non-black, chronic HBV co-infection, negative HIV-status and high CD4 counts.
in HIV-positives (17;18). After 20-30 years of chronic infection without treatment, serious complications of the liver can develop; it has been estimated that liver cirrhosis occurs in 6-25% of the patients, of whom 1-4% develop hepatocellular carcinoma (16;18). Although HCV is a slow progressive disease, it is the main indication for liver transplantation in the United States (3).

**HCV treatment**
Standard antiviral treatment of chronic HCV consists of weekly pegylated interferon injection with a daily oral dose of ribavirin. Depending on the genotype treatment duration is usually 12-24 weeks (genotype 2 and 3) or 24-48 weeks (genotype 1 and 4). Successful treatment outcome consists of reaching a sustained virological response (SVR), which is defined as undetectable HCV RNA 24 weeks after the end of treatment (16). Genotypes 1 and 4 are more difficult to treat, with a successful treatment outcome of 40-60% in the absence of HIV infection, while 60-80% of genotypes 2 and 3 have a successful treatment outcome. Treatment outcome improves when treatment is started shortly after acute HCV infection in both HCV co-infected and HCV monoinfected individuals (19;20).

The majority of patients on HCV treatment experience serious side effects, which include flu-like symptoms, depression, and fatigue (21;22). Because of this, 10-15% of patients discontinue their treatment. IDU are considered a difficult that is difficult to treat, because they lack adherence and the risk for re-infection is high (23). Since 2005 the Amsterdam Public Health Service treats HIV-negative IDU successfully, as described in chapter 4.1 and others have also managed successful treatment using a multidisciplinary approach (24). New treatment options approved by the FDA in 2011 for genotype 1 and will be reimbursed by insurance companies in the Netherlands from April 2012 onwards. This new medication consists of two protease inhibitors (direct-acting antivirals - DAAs), telaprevir and boceprevir, which directly target viral enzymes and influence host-virus interactions. One of these medications can be added to the current treatment regime with peginterferon alfa and ribavirine (25). Although both protease inhibitors generate side effects, treatment outcome is much improved; SVR increases from 50-70% (26). However resistance to the medication can cause treatment failure. In the nearby future more combinations, also in the absence of interferon, will become available (27).

**HIV/HCV co-infection**
HCV and HIV share their routes of transmission and therefore around 12.5% of HIV-infected persons are co-infected with HCV (28). HIV/HCV co-infection negatively influences the natural course of HCV infection, in particular when HCV is acquired after HIV and at an older age (>40 years) (29). HIV/HCV co-infection is associated with lower rates of spontaneous viral clearance of HCV, accelerated progression to liver disease and a less favourable HCV treatment outcome (30). There are still inconsistent results as to whether HCV has an effect on HIV infection (31-33). HCV can cause hepatotoxicity in combination with certain types of HIV medication, causing a forced switch or stop of HAART (34). HCV antiretroviral therapy achieves a sustained virological response in less than 30% of HIV-positive individuals chronically infected with HCV genotypes 1 and 4, and in 44-73% of those with HCV genotypes 2 and 3 (35). However, more successful response rates are reported for HIV-positives treated during the acute phase of HCV infection (19).
Prevention
No vaccination is available to prevent HCV infection. Prevention should be sought in terms of primary (avoidance of infection), secondary (detection of disease at an early stage) and tertiary (reduction of disease progression) prevention. Avoidance of HCV infection includes a change of risk behaviour, e.g. ceasing to inject drugs, or participating fully in harm reduction, e.g. through a needle exchange program and methadone prescription (36). Screening those who are at risk for HCV infection will lead to early detection of the virus. Early detection and treatment of HCV during the acute phase has been associated with a more favourable HCV treatment outcome (19). In addition, successful treatment prevents secondary infection (tertiary prevention), however, continued risk behaviour creates a risk of HCV reinfection.

Molecular epidemiology

HCV genotyping
Worldwide there are 6 major genotypes. Some are found globally due to needle sharing among injecting drug users (types 1a and 3a) or contaminated blood products (types 1b, 2a and 2b) and represent the majority of infections in Europe and northern America. Other subtypes of the genotypes are more restricted to the endemic geographic area where they are spread; Africa and the Middle East (genotypes 1,2 and 4) and Southeast Asia (genotype 2 and 6) (37-39). As HCV genotype distribution depends on geographical area, mode of transmission, and its genetic variation increases over time, it provides information about the historical origin and spread of the virus (37;40;41).

Phylogenetic analysis
The degree of genetic diversity among different HCV viral variants provides information regarding the time that has passed since two viruses separated from a common ancestor, and hence the likelihood that two strains were acquired in the context of the same transmission network. Molecular epidemiology can therefore be used as a tool to identify the common source of infection (40-42). Dissimilarity between viral variants is often expressed as the genetic distance, and these dissimilarities can be caused by a mutation of the genetic genome. The genetic distance among genes of different HCV viral strains can be represented in a phylogenetic tree, comparable to a pedigree showing which genes are most closely related (see figure 2). The genetic distance between HCV strains can be calculated and consequently a phylogenetic tree can be built. When HCV strains share a common ancestor they are connected through a node in the phylogenetic tree (as is shown in figure 2). When HCV strains are closely related they are shown as a cluster in the phylogenetic tree which suggests a common source of infection and, moreover, the transmission route (e.g. parenteral, sexual) (41).
The Netherlands

In the Netherlands little is known about HCV prevalence among the general population. Based on extrapolation of selected groups, including mainly new blood donors, HCV prevalence is estimated at 0.1-0.4% which corresponds to 16,000-65,000 HCV infected individuals (44). Identified risk groups in the Netherlands are: IDU (prevalence: 47-79%) (45;46), recipients of blood and blood products before 1991 (prevalence: 0.17%) (45), haemodialysis patients (prevalence: 55%) (47), individuals who underwent medical procedures abroad (prevalence depends on the country of origin), sexual and household partners of chronic HCV carriers (prevalence unknown), and children born to HCV infected mothers (prevalence: 4-20%, depending on the HIV-status of the mother) (11;48). Since 2000 HIV-positive MSM have also been identified as a risk group for HCV, with sexual contact as the main transmission route in this group (13). Screening the general population could be considered; however, such a screening program would not be cost-effective because of the low prevalence in the Netherlands. On the other hand, cost-effectiveness may be enhanced if implemented as part of an already existing screening program. Pregnant women are routinely screened for several infectious diseases in their 10-12th week of pregnancy, so it would be interesting to investigate whether adding HCV screening would be viable in this regard. Results in this area are further described in chapter 5.1.

Figure 2: Schematic example of a rooted phylogenetic tree. Branches connect the internal nodes that represent the most common recent ancestor. Genetic distance can be calculated by summing up the horizontal branch lengths. The nodes represent the most recent ancestor. Shaded boxes reflect HCV subtype variation and shaded circles reflect HCV subtype variation, which are slightly genetically distinct from each other (figure adapted from (43)).
Amsterdam Academic Collaborative Centre on Public Health (Sarphati initiative)
The Amsterdam Academic Collaborative on Public Health (Sarphati initiative) was initiated in 2006 and is funded by ZonMW (The Netherlands Organization for Health Research and Development). It is a partnership between the Public Health Service of Amsterdam and the Academic Medical Centre of the University of Amsterdam, consisting of two networks; the infectious diseases network and the epidemiology network. The aim of the infectious diseases network is to build up and sustain an infrastructure that will facilitate:

a. Demand driven public health research on new and re-emerging infectious diseases,

b. Knowledge transfer of results to public health/medical professionals and students,

c. A scientific approach to demands that derive from public health service practices.

The Collaborative will contribute to more evidence-based service practices in prevention and control programmes for infectious diseases. As part of the general cooperation within the network, which comprises various structural arrangements (unified leadership, double appointments of senior-and junior staff, education, and network meetings), three specific PhD projects were started. This thesis is the outcome of one of these three PhD programmes:

Since HCV prevalence among the general population in the Netherlands has been estimated based on limited data, the size of and HCV prevalence among current risk groups are unknown (49), and there are now improved treatment options, the Health Council revised its 1997 recommendations in 2004 and recommended conducting epidemiological studies in order to gain more insight into the current situation in the Netherlands (44). In line with this recommendation, the Amsterdam Academic Collaborative Centre on Public Health (Sarphati initiative) initiated research which could lead to an evidence-based policy on the spread of HCV in the Netherlands, in order to develop and implement new screening and treatment programmes, identify (new) risk groups living with HCV, and estimate the impact and burden of disease of HCV infections. The results of this initiative are outlined in this thesis.

Outline of this thesis

The studies in this thesis were performed to improve our understanding of the spread and impact of HCV in the Netherlands using a multidisciplinary approach. Using epidemiological, virological and clinical data we studied the spread and determinants of HCV among the general population and presumed high risk groups included HIV-infected individuals, migrants and people with multiple tattoos and piercings. In addition, we evaluated the uptake and outcomes of HCV screening and treatment in IDU and estimated the future burden of disease in this group. Lastly, we examined whether HCV screening is cost-effective for pregnant women. In table 1 different data sources, study populations, and their study period are outlined.

HCV screening programs have been developed and implemented throughout the world, all within their own setting. Effective screening programs are urgently needed to provide undiagnosed HCV-infected individuals with therapy. In chapter 2, literature was systematically reviewed to examine characteristics and outcomes of HCV screening programs and focuses on strategies to identify HCV risk groups hidden among the general population.

Chapter 3 describes the HCV epidemiology of sub-populations in the Dutch population and includes three studies on HCV in MSM. The first study is a review on hepatitis A/B/C in the MSM population. The second study describes the HCV prevalence and determinants among HIV-positive and HIV-negative MSM participating in a biannual survey of the STI outpatient clinic located at
the Amsterdam Public Health Service. In the third study the HCV incidence was calculated over a 15 year period (1995-2010) in the same setting. In the last two studies phylogenetic analysis was used to examine the transmission routes of HCV in MSM.
Other studies included in this chapter describe the HCV prevalence among migrants and among people with multiple tattoos and piercings. The first study is performed among Dutch, Western and non-Western migrants, with a special focus on the three largest migrant groups living in the Netherlands; people originating from Surinam, Morocco and Turkey. The second study describes the HCV and HBV prevalence among tattoo and piercing artists and people with multiple tattoos and piercings. According to literature this group is at high risk for HBV and HCV. In this study we examine whether this is true for the Netherlands.

In the first study of Chapter 4, results of an HCV program offering HCV testing and treatment in a multidisciplinary setting targeted at IDU with chronic HCV (Drug Users Treatment Chronic Hepatitis-C, DUTCH-C) are described. The second study predicts the future burden of disease in the IDU group and the role of HCV treatment and HIV co-infection.

Chapter 5 describes a cost-effectiveness analysis of implementing HCV screening in a low prevalence population; pregnant women. In the general discussion, Chapter 6, main findings concerning the spread of HCV among the different risk groups in the Netherlands are discussed and related to recent literature. The implications of the findings for prevention and public health policy and interventions are discussed, and recommendations for future research are presented.
Table 1: Data sources used in this thesis

<table>
<thead>
<tr>
<th>Data sources</th>
<th>Study population</th>
<th>Study period</th>
<th>Chapter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bi annual HIV survey STI outpatient clinic PHSA</td>
<td>Men who have sex with men</td>
<td>2007-mid 2008</td>
<td>3.1.2</td>
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<tr>
<td>Bi annual HIV survey STI outpatient clinic PHSA</td>
<td>HIV-positive and HIV-negative MSM</td>
<td>1995-2010</td>
<td>3.1.3</td>
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<tr>
<td>Bi annual HIV survey STI outpatient clinic PHSA</td>
<td>Heterosexual men and women</td>
<td>2007-mid 2009</td>
<td>3.2</td>
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<td>Random sample pregnant women region Amsterdam</td>
<td>Pregnant women</td>
<td>2003</td>
<td>3.2;5.2</td>
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<tr>
<td>Amsterdam Health Monitor</td>
<td>Random sample general population of Amsterdam</td>
<td>2004</td>
<td>3.2</td>
</tr>
<tr>
<td>PIENTER 2 study (RIVM)</td>
<td>Random sample general population of the Netherlands</td>
<td>2006-2007</td>
<td>3.2</td>
</tr>
<tr>
<td>Bi annual HIV survey STI outpatient clinic PHSA</td>
<td>Heterosexual, non-IDU visitors with ≥2 tattoo/piercing</td>
<td>November 2008-April 2009</td>
<td>3.3</td>
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<tr>
<td>Survey at tattoo conventions and tattoo and piercing shops</td>
<td>Heterosexual, non-IDU participants with ≥2 tattoo/piercing or being a tattoo or piercing artist</td>
<td>2008-2010</td>
<td>3.3</td>
</tr>
<tr>
<td>DUTCH-C</td>
<td>Amsterdam Cohort studies together and drug users referred to the Drug Users Treatment for Chronic Hepatitis-C unit.</td>
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<td>4.1</td>
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<tr>
<td>Amsterdam Cohort Studies (ACS)</td>
<td>HCV-positive IDU</td>
<td>1985-2005</td>
<td>4.2</td>
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References


(41) van de Laar TJW. Molecular epidemiology of hepatitis C Virus, dissertation 2008.


