Viral hepatitis among men who have sex with men, epidemiology and public health consequences

A T Urbanus (aurbanus@ggd.amsterdam.nl)[1], R van Houdt[1], T JW van de Laar[1], R A Coutinho[2,3]

1. Cluster Infectious Diseases, Public Health Service, Amsterdam, the Netherlands
2. Centre for Infection and Immunology Amsterdam (CINIMA), Academic Medical Centre (University of Amsterdam), Amsterdam, the Netherlands
3. National Institute for Public Health and the Environment, Centre for Infectious Disease Control (RIVM), Bilthoven, the Netherlands

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Viral hepatitis causes major disease burden worldwide, due to the chronic hepatitis sequelae: cirrhosis and primary liver cancer. Transmission of viral hepatitis is a problem not only in low-income countries, but also in high-income ones where viral hepatitis is a frequently occurring infection among men who have sex with men (MSM). Although the transmission routes of the three main hepatitis viruses, A, B and C, differ, MSM mainly acquire viral hepatitis during sexual contact. Vaccination programmes (only available for hepatitis A and B), raising awareness, and screening can be used to prevent transmission. However, despite the introduction of such methods in many high-income countries, the spread of viral hepatitis among MSM is still ongoing. This paper provides an overview of sexually acquired hepatitis A, B, and C among MSM in high-income countries, using recent insights obtained through molecular epidemiology, with the aim to raise awareness, improve vaccination coverage, and stimulate prevention programs.

Introduction

Worldwide, more than two billion people are infected with viral hepatitis A, B or C (HAV, HBV or HCV, respectively). Although the clinical symptoms of these infections are largely similar and include fever, malaise, and jaundice, their frequency and severity differ. HAV is symptomatic mainly in adults, whereas infections with HBV and especially HCV are often asymptomatic. The transmission routes of HAV, HBV, and HCV also differ: HAV spreads through faecal-oral contact, HBV is transmitted by blood contact as well as by sexual contact, and HCV is mainly transmitted by blood contact [1-3]. HAV is self-limiting, a fulminant course of infection is rare and the case fatality rate is low (0.3%). In contrast, 5-10% of adults with acute HBV infection and 50-80% of individuals with acute HCV infection develop persistent viraemia [4, 5]. Over decades, chronic infection with HBV and HCV can lead to liver cirrhosis, hepatocellular carcinoma and eventually death. Spontaneous viral clearance of HAV and HBV, but not HCV, results in life-long immunological protection. HCV re-infection, on the other hand, is frequently observed in individuals with ongoing risk behaviour [6].

In high endemic countries, HAV is mainly transmitted by close contact or as a result of inadequate sanitation (e.g. ingesting contaminated food or water), HBV is mainly transmitted at birth or during early childhood whereas new HCV infections are often health-care associated. In contrast, the majority of new HBV and HCV infections in low endemic countries occur within specific risk groups. HBV spreads among drug users and sexual risk groups, such as men who have sex with men (MSM) and commercial sex workers, whereas HCV has been traditionally restricted to injecting drug users and, before donor screening was introduced, to recipients of blood and blood products. In low endemic areas, new HAV infections occur mostly among travellers returning from high endemic places, causing small outbreaks among unvaccinated children or adults at, for example, child care centres, or among MSM via oro-anal contact [1-3].

There is no specific treatment available for HAV. For chronic HBV carriers treatment includes interferon and nucleoside analogues, while pegylated-interferon, in combination with ribavirin, is available for chronic HCV [1, 2]. For both viruses, but especially chronic HBV, treatment does not always result in viral eradication. An effective vaccine, which gives 20 years to life-long protection, is available for HAV and HBV, while no vaccination is as yet available for HCV, meaning that prevention relies totally on precautionary measures that prevent its further spread [1-3].

In this article, we provide an overview of sexually acquired viral hepatitis among MSM, using recent insights obtained through molecular epidemiology of HAV, HBV, and HCV. In addition we want to stress that, among MSM, awareness and risk perception regarding viral hepatitis needs to be improved in order to increase vaccination coverage and limit further spread of these viruses among the MSM community.

Hepatitis A

In high-income countries such as those in Western Europe and North America, HAV is rarely contracted during childhood, therefore the majority of adults are susceptible to the infection. Individuals living in low endemic countries can contract HAV when they travel to developing countries where the virus still circulates widely. HAV has for many years also been recognised as a sexually transmitted infection (STI), especially among MSM. In Scandinavia – one of the first areas where the incidence and prevalence of HAV declined strongly - outbreaks of hepatitis A among MSM were already reported about three decades ago [7, 8]. In a cohort study of MSM in Amsterdam, performed at the time of the Scandinavian outbreaks, 42% of 689 MSM tested positive for HAV antibodies.

HAV prevalence was shown to increase with the time the person had been homosexually active, and strongly exceeded the prevalence in the general population [9]. Among susceptible MSM, the HAV incidence was about 7% per year and correlated with the number of sexual partners. Other early studies identified oro-anal sexual contact as the most likely transmission route among MSM [10]. In recent years, outbreaks of hepatitis A among MSM have been described in most high-income countries [11].

The molecular typing of HAV isolates is used to gain a better insight into how HAV spreads among the population. In a study in Amsterdam in 2000-2002, HAV isolated from stool samples of acute HAV cases was amplified and sequenced [12]. Two separate transmission chains with little mutual interrelation were found: one among MSM (mostly genotype 1A) and another among travellers from HAV-endemic countries (genotype 1B and genotype 3). The patterns of HAV introduction and transmission in these groups were further investigated, using cluster analysis based on the genetic distances between the HAV isolates obtained during the acute phase of infection [13]. Large clusters were found among MSM, indicating the ongoing spread of specific HAV viruses among this group.

Among travellers, introductions of new HAV strains from endemic countries occur regularly, especially after the summer holidays. Transmission to close contacts occurs on a limited scale. These outbreaks are usually detected early and stopped through preventive measures (vaccination).

Recently, a collaborative European study was undertaken to determine if HAV strains that cause outbreaks among MSM in different countries are genetically related [11]. By comparing sequences, it was shown that the majority of strains found among MSM in the participating European countries formed closely related clusters belonging to genotype 1A. Similar strains found among MSM during a nearly 10-year period (1995-2005) indicated that these specific strains have been circulating among this risk group for a long time. This shows that HAV is transmitted through sexual networks of MSM throughout Europe and possibly other high-income countries.

Although co-infection of HIV and HAV suggests no impact of HAV infection on the progression rate of HIV, HIV-positive patients co-infected with HAV should be carefully monitored since their HAV infection is more likely to be symptomatic and of longer duration [14]. There is also evidence for a higher lever of viraemia [15]. However, depending on the CD4 count (>200 cells/mm^3), HIV infection does not influence the outcome of acute hepatitis A [14].

Hepatitis B

Transmission of HBV is a problem not only in highly endemic countries, but also in low endemic countries with a low HBV prevalence and incidence. In these countries, transmission of HBV occurring at birth or during early childhood is rare, and the infection is mainly restricted to specific risk groups, such as MSM who acquire HBV mainly through sexual contact [16]. Injecting drug use (IDU) remains an important risk factor for HBV transmission, especially in eastern European countries. However, a decline in IDU HBV cases has been observed in many high-income countries in the past decade [17].

HBV can be transmitted through mucosal contact, making it not only a blood-borne virus, but also an STI. HBV has been recognised as an important STI among MSM for many years, especially as HBV is far more infectious than HIV. The HBV incidence among MSM is estimated to be twenty times higher than among the general population. The high prevalence, together with the increased transmission rates associated with unprotected anal intercourse, makes MSM more prone to becoming infected with HBV than the heterosexual population.

In the 1980s, a steep decline was observed in HBV incidence among MSM [18, 19]. From the 1990s to date, the incidence has remained stable at a low level with some small fluctuations. The steep decline in the 1980s probably reflected a decrease in sexual risk behaviour among MSM caused by HIV/AIDS awareness. No such change in incidence was observed for HAV, most likely due to ongoing transmission through the faecal-oral route and since the perception of the risk of an HAV infection is low. HCV incidence follows a different course, which is described in the next paragraph.

Recent molecular epidemiological studies have shown that an identical HBV genotype A strain has been circulating among MSM for many years. This is not only the case in Europe, for example, in the United Kingdom and the Netherlands, but also in other countries around the globe, like Japan [19-21]. For HAV and HCV, several studies have shown that there is ongoing transmission of several different MSM-specific viral strains within MSM networks [11,22]. Thus far, research indicates that just one HBV strain circulates among MSM in high-income countries. A reason for this could be that genotype A is the predominant genotype in many of these high-income countries. Furthermore, due to the high stability of the HBV genome, it is hard to make a clear distinction between new introductions and ongoing transmission of certain strains compared to HAV and HCV. Another reason could be that in these studies, only the S-gene was sequenced, therefore, regarding the low variability in the genome, it might be better to do full genome sequencing analyses. To ascertain whether this single genotype A strain is the only strain circulating among the majority of MSM in high-income countries, further international collaboration, including testing of samples from a larger set of countries, is needed.

In the MSM community, 6-10% of HBV-infected men are co-infected with HIV [23]. HBV is more progressive in HIV-positive patients, and both the HBV carrier rates and the viral load are higher. The episodes of HBV activation are also more frequent, cirrhosis occurs more rapidly and hepatocellular carcinoma is more frequent than in HBV mono-infected patients [23]. When there is co-infection with HIV, HBV treatment options are limited and treatment outcomes are negatively influenced. Mono-therapy for both HIV and HBV is not appropriate due to the high possibility of resistance [23]. Since many of the antiviral agents used for HBV treatment are included in the HAART regiment against HIV as well, caution should be taken when starting treatment for either HBV or HIV.

Hepatitis C

HCV is primarily transmitted by exposure to infected blood. In high-income countries, parenteral risk factors, particularly IDU, now account for the vast majority of HCV transmissions [1]. Even in the presence of HIV co-infection, HCV is rarely transmitted through heterosexual intercourse [24]. However, recent outbreaks of acute HCV among HIV-positive MSM who deny IDU suggest that the epidemiology of HCV transmission is changing in this population. In several European countries [25-27] as well as in the United

States [28] and Australia [29], HCV has unexpectedly emerged as an STI among HIV-positive MSM. 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 Amsterdam, 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 [27]. The HCV prevalence among HIV-positive MSM visiting the STI clinic in Amsterdam reached an alarming 15-20% in the period 2007-2008, versus an estimated 1-4% before 2000. HCV prevalence found among HIV-negative MSM was significantly lower (0.4%) in this study [30]. Also in London, the estimated annual HCV-incidence in HIV-positive MSM attending HIV and sexual health clinics rose by 20% each year to 12 per 1,000 person years in the first six months of 2006 [31]. To what extent HCV affects communities of HIV-positive MSM in other high-income countries remains unclear.

Molecular typing of HCV isolates confirmed the presence of MSM-specific transmission networks in London [25], Paris [26] and Amsterdam [27]. A collaborative phylogenetic study revealed that these locally reported outbreaks were in fact part of one larger interconnected European transmission network [22]. MSM-specific HCV strains, mainly of difficult-to-treat HCV genotypes 1 and 4, were detected in 86% of European MSM with acute HCV. Once introduced, these strains rapidly spread to neighbouring countries; in fact, 74% of European HCV/HIV co-infected MSM were infected with MSM-specific strains that circulated in more than one European country. In contrast, the HCV outbreak in Australia showed very limited overlap with the transmission network in Europe, and has a (much) larger proportion of infections attributable to concomitant IDU [22, 29].

The sudden emergence of HCV as an STI among HIV-positive MSM is poorly understood. As multiple strains of different HCV genotypes circulate among HIV-positive MSM, this suggests a behavioural change in MSM rather than evolution of the virus into a more virulent variant. Evolutionary analysis confirms that HCV had been introduced into the population as early as the 1980s, most likely from the IDU-scene, but its actual spread only started after 1996 [22]. This coincides with the introduction of HAART, which was followed by a decline in HIV risk perception and a rise in sexual risk behaviour among MSM [32]. Only one case-control study with detailed information on risk behaviour has examined its independent relation with acute HCV [25]. This study suggests that in the context of (traumatic) sexual practises, permucosal risk factors were associated with acute HCV infection. Rough sexual techniques, such as fisting; a higher number of sexual partners and group sex; co-infection with ulcerative STI such as syphilis, herpes, and lymphogranuloma venereum (LGV); sex under the influence of drugs (especially when applied anally); the use of rectal enema; and the presence of haemorrhoids have been identified as potential risk factors for sexually acquired HCV [25,30,33]. However, these factors cannot explain why there was no evidence of sexual transmission in the 1980s, a period in which STI and sexual risk taking were highly prevalent among MSM [27].

Nearly all MSM with acute HCV are co-infected with HIV. HIV infection might facilitate HCV transmission by increasing viral infectiousness through higher HCV viral loads in blood and semen [34] as well as viral susceptibility through HIV-impaired immunological control [35]. Even in the presence of preserved overall CD4 counts (>500 cells/mm^3), massive irreversible damage already occurs to the mucosal tissues of the gastrointestinal immune system in the first weeks of HIV infection [36] which could facilitate HCV entry through the mucosa. Moreover, serosorting (engaging in sexual contact with partners of the same HIV serostatus), which is considered a risk reduction strategy for HIV transmission, might fuel the epidemic of other STI, including HCV [37].

The emergence of HCV among HIV-positive MSM has serious clinical implications. 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) [28]. HIV/HCV co-infection is associated with lower rates of spontaneous viral clearance, accelerated progression to liver disease and less favourable treatment outcome [38]. HCV antiretroviral therapy achieves sustained virological response in less than 20% of HIV-positive individuals chronically infected with HCV genotypes 1 and 4. However, more favourable response rates have been reported for HIV-positive MSM treated during the acute phase of HCV infection [39].

Preventive measures against viral hepatitis in MSM

In high-income countries, MSM apparently are a major risk group for viral hepatitis. Several studies have shown that MSM-specific strains of HAV, HBV, and HCV circulate among the MSM community, strongly suggesting the presence of MSM-specific networks driven by sexual contact [11-13, 18-22, 26, 30, 40].

Universal vaccination for HAV is only recommended by the WHO in intermediate endemic countries; low endemic countries are advised to limit vaccination to risk groups, like MSM [41]. However, only a few high-income countries have implemented targeted vaccination campaigns for HAV. According to Jacobs *et al.*, the cost-effectiveness of the HAV/HBV combination vaccine in high-risk groups is higher than that of the HBV vaccine alone [42]. Therefore, to increase the HAV coverage, HAV vaccination should be considered for implementation within the existing HBV campaigns for MSM.

Preventive measures for HBV among MSM consist of vaccination and awareness campaigns as well as screening for chronic infections. Vaccination of close contacts and treatment of chronically infected patients reduce the number of secondary infections. Treatment of chronic HBV carriers is also in the interest of the infected patient, as it prevents the long-term sequelae of HBV. Despite the introduction of an effective vaccine more than 25 years ago and the implementation of universal or behavioural risk group vaccination strategies in most high-income countries years ago, HBV is still endemic among MSM. A reason for this ongoing transmission among MSM is that universal vaccination programmes among newborns, with or without catch-up vaccination among adolescents, have up till now left the adult MSM population at risk. Targeted vaccination fails to reach a substantial proportion of MSM at risk and appears to be insufficient to reduce the incidence among this group [43, 44]. Consequently, independent of the various countries' current prevention strategies, the majority of MSM will remain at risk of HBV infection for at least the next decade. Universal vaccination will eventually prevent the ongoing transmission of HBV among MSM, depending on the coverage of these programmes. In the meantime, efforts should be directed towards promoting the HBV vaccination of MSM as early as possible after they become sexually active and targeted at those who are at greatest risk [45].

HBV co-infection in individuals living with HIV increases liver-related mortality and morbidity, toxicity of antiretroviral therapy, and complicates treatment decisions. Therefore, all HIV-infected MSM should receive HBV vaccination. However, the response rate to HBV vaccination is lower (18-71%) and HIV-infected MSM are also less likely to achieve and maintain high (protective) anti-HBs titres [46]. The response rate to HAV vaccination in HIV-infected patients is also lower compared to immunocompetent individuals. The low CD4 cell count and not yet being on HAART are the two main reasons for this low response rate [46, 47]. Administrating higher vaccine doses, revaccination, or postponing vaccination until HAART reaches a higher CD4 count are the current strategies to achieve higher response rate to HAV and HBV vaccination [46, 48-50].

Depending on future improvements in treatment, systematic screening of the MSM population for chronic HBV infections might be feasible. In countries with a targeted vaccination strategy, screening for HBV is automatically embedded in the programme [43]. Screening of migrants, even those with a low HBsAg prevalence (2.2%), has been shown to be cost-effective, because early detection of chronic infections and referral of chronic carriers has a positive impact on liver-related health outcomes and prevents secondary infections [51]. Since in some countries, the HBsAg prevalence among MSM is comparable or even higher than in migrant populations, it is likely that HBV screening of MSM is cost-effective, as well.

Since no vaccination is available for HCV, HIV-infected MSM should be regularly screened for HCV infection. Early detection and treatment of HCV during the acute phase has been associated with a more favourable HCV treatment outcome [39]. Successful treatment prevents secondary infections to HIV-positive sexual contacts and could possibly prevent spill-over to the HIV-negative population [31]. In contrast to HCV screening of the general population, HCV screening of groups with an elevated risk, like IDU, is cost-effective [52]. HIV-infected MSM have now also been recognised as a high risk group for HCV infection. Therefore, screening of this group might also be cost-effective. Screening for HCV infection could be done regularly by, for example, an HIV specialist or at STI clinics for early diagnosis. STI clinics, especially, have the means, the knowledge and the reach to inform high-risk groups about emerging STI like HCV. In addition, because HAV is not yet well known as an STI, promotion of HAV vaccination should be stimulated.

Concluding remarks

Failure to control the spread of HBV among MSM despite the long-term availability of an effective vaccine indicates that vaccines alone are not sufficient to control STI among high-risk groups. Increasing risk perception and awareness of the clinical consequences of STI is essential. Nevertheless, in practice it appears to be difficult to reach MSM who are at high risk of STI, as many do not consider themselves to be at risk or are unaware of the severe clinical consequences of some STI. To limit the spread of viral hepatitis among MSM, raising awareness and increasing risk perception needs to be combined with vaccination programmes.

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