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REVIEW

Sexually transmitted hepatitis C virus infections: current trends, and recent advances in understanding the spread in men who have sex with men

Bernadien M Nijmeijer[1], Jelle Koopsen[2], Janke Schinkel[2], Maria Prins[3§*] and Teunis BH Geijtenbeek[1§*]

[§]**Corresponding authors**: Teunis BH Geijtenbeek, Department of Experimental Immunology, Amsterdam Infection and Immunity Institute, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands. Tel: +31-20-566 8590. (t.b.geijtenbeek@amc.uva.nl)
Maria Prins, Department of Infectious Diseases, Research and Prevention, Public Health Service of Amsterdam, Amsterdam, The Netherlands. Tel: +31205555243. (mprins@ggd.amsterdam.nl)
*These authors contributed equally to this work.

Abstract

Introduction: Hepatitis C virus (HCV) is a major public health threat. Although the recent availability of highly effective directly acting antivirals created optimism towards HCV elimination, there is ongoing transmission of HCV in men who have sex with men (MSM). We here report current epidemiological trends and synthesise evidence on behavioural, network, cellular and molecular host factors associated with sexual transmission of HCV, in particular the role of HIV-1 co-infection. We discuss prevention opportunities focusing on the potential of HCV treatment.

Methods: We searched MEDLINE, fact sheets from health professional bodies and conference abstracts using appropriate keywords to identify and select relevant reports.

Results and discussion: Recent studies strongly suggest that HCV is transmitted via sexual contact in HIV-positive MSM and more recently in HIV-negative MSM eligible for or on pre-exposure prophylaxis. The reinfection risk following clearance is about 10 times the risk of primary infection. International connectedness of MSM transmission networks might contribute to ongoing reinfection. Some of these networks might overlap with networks of people who inject drugs. Although, the precise mechanisms facilitating sexual transmission remain unclear, damage to the mucosal barrier in the rectum could increase susceptibility. Mucosal dendritic cell subsets could increase HCV susceptibility by retaining HCV and transmitting the virus to other cells, allowing egress into blood and liver. Early identification of new HCV infections is important to prevent onward transmission, but early diagnosis of acute HCV infection and prompt treatment is hampered by the slow rate of HCV antibody seroconversion, which in rare cases may take more than a year. Novel tests such as testing for HCV core antigen might facilitate early diagnosis.

Conclusions: High-risk sexual behaviour, network characteristics, co-infection with sexually transmitted infections like HIV-1 and other concomitant bacterial and viral sexually transmitted infections are important factors that lead to HCV spread. Targeted and combined prevention efforts including effective behavioural interventions and scale-up of HCV testing and treatment are required to halt HCV transmission in MSM.

Keywords: hepatitis C virus; sexual transmission; men who have sex with men; epidemiology; dendritic cells; prevention

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1 | INTRODUCTION

In 2015, viral hepatitis was responsible for an estimated 1.3 million deaths from acute infection and hepatitis-related liver cancer and cirrhosis – a toll comparable to that of HIV and tuberculosis [1]. Hepatitis C virus (HCV) infections account for almost 30% of these deaths. Worldwide most HCV infections have been acquired by exposure to infected blood or blood products. After the first commercial test became available in 1991 and HCV transmission through blood product was effectively halted, sharing of injecting equipment among people who inject drugs (PWID) became the major route of transmission in high-income countries [2]. In contrast to hepatitis B, the risk of sexual transmission of HCV has always been considered low [3,4]. This low risk was confirmed by a recent study among 500 anti-HCV-positive, HIV-negative persons and their long-term HCV-negative heterosexual partners, reporting a maximum incidence rate of HCV transmission by sex of 0.07% per year or one infection per 190,000 sexual contact, and a lack of association with specific sexual practices [5]. However, in the mid-2000s, HCV infection emerged in men who have sex with men (MSM) [6],

likely due to sexual contact [7]. Although there was skepticism among some investigators, who assumed the cause was under-reporting of injecting drugs, further evidence from Europe, the United States and Australia that MSM who denied injecting drug acquired HCV [8,9], reopened the discussion on the importance of sexual transmission of HCV [7]. The high reinfection rates among MSM who cleared HCV spontaneously or who were successfully treated [10-12], further underscored the importance of sexual behaviour in HCV transmission. As new HCV infections were typically found in HIV-positive MSM, it was initially suggested that HIV-1 status could be an important factor for sexually acquired HCV [10,13-15]. However, recent studies suggest that sexual transmission of HCV also occurs in HIV-1-negative MSM eligible for or using pre-exposure prophylaxis (PrEP), indicating that HIV-1 infection status is not the only factor affecting susceptibility [16-18]. The frequency of exposure to HCV within specific sexual networks is also important as recent studies show that HIV-negative MSM are infected with HCV-strains already circulating among HIV-positive MSM [19-21]. Although directly acting antiviral (DAA) treatment is very effective in clearing HCV [22], and its availability created optimism towards HCV elimination, the high HCV (re)infection rates, likely via sexual contact, highlight the need for a better understanding of the mechanisms involved in sexual transmission of HCV.

We reviewed the current knowledge regarding HCV infection in MSM to summarize epidemiological trends and synthesise evidence on behavioural, network and host factors associated with sexual transmission of HCV. We also discuss prevention opportunities focusing on the potential of HCV infection treatment programmes on the spread of sexually acquired HCV.

2 | METHODS

We have systemically searched MEDLINE, fact sheets from health professional bodies including the World Health Organization, Center for disease Control and Prevention, the American Association for the Study of Liver Diseases and recent conference abstracts, published in English before January 2019. We have searched these databases using the following keywords: HCV, acute HCV, sexual transmission, MSM, HIV-1 coinfection, DAA, PrEP, reinfection, molecular epidemiology, HCV diagnosis, HCV treatment guidelines, phylogenetics and phylogeography to identify and select relevant reports.

2.1 | Epidemiology of sexually transmitted HCV

2.1.1 | Trends in HCV infections in HIV-positive and -negative MSM

Outbreaks of sexually transmitted HCV have been reported globally among HIV-positive MSM since 2000 [7,23]. Using data from the international CASCADE collaboration, it was found that HCV incidence among HIV-positive MSM significantly increased from 0.07/100 person-years in 1990 to 1.8 per 100 person years in 2014 [24]. These findings are in line with the incidence rates and the time trend observed in a meta-analysis pooling incidence data from 17 individual studies [10]. Trends differed per European region: while HCV incidence has stabilized in western Europe, likely due to increased awareness, testing and uptake of therapy, it continues to increase in northern Europe [24]. Furthermore, time from HIV to HCV infection has shortened in recent years [24]. The risk of reinfection is more than 10 times higher than primary infections, which is of great concern [10]. The European NEAT study, including data from eight centres in Austria, France, Germany and the UK, reported an overall reinfection incidence of 7.3/100 person-years in HIV-positive MSM who spontaneously cleared their HCV infection, which occurs in approximately 15% of acute HCV infections in HIV-positive MSM [25], or responded to treatment [12]. These findings are in line with studies from Australia and elsewhere in Europe, showing that up to one-third acquired a reinfection within two years [11,26-28]. Temporal trends in the incidence of HCV reinfection have not been investigated, with exception of one recent study from Canada showing that reinfection rates did not diminish over time [29]. Reinfection rates in this study were about half the rates observed in studies from Europe and Australia, indicating that infection rates might be regional specific [29].

In contrast to HIV-positive MSM, HIV-negative MSM are generally not in routine clinical care. Hence, data on HCV incidence are more difficult to obtain. Meta-analyses estimated a 4-to-19-fold times lower HCV incidence in HIV-negative MSM compared to their HIV-positive counterparts and a pooled incidence rate of 0.04-0.15/100 person-years in HIV-negative MSM [30-32]. This is comparable to the incidence observed among HIV-positive MSM in the early 1990s [10,24]. The HCV prevalence among HIV-negative MSM ranged between 0.3% and 1.5% in studies published from 2012 to 2018 [33-40]. These data suggest that HV-negative men remain largely unaffected by the outbreak of HCV among HIV-positive MSM. A higher prevalence (3-4%) was found in studies from Canada and the U.S., but HCV infections were strongly associated with lifetime injecting drug use [41,42]. Data on a rise in HCV incidence among HIV-negative MSM are limited and inconsistent [7]. A serial cross-sectional study among HIV-negative MSM attending a large clinic treating sexually transmitted infections (STI) in the Netherlands showed a stable HCV prevalence (about 1% each year) over the period 2007-2017 [39], suggesting HCV incidence is not increasing in this group. Recently, an unexpectedly relatively high anti-HCV prevalence (4.8%) was found at PrEP initiation among MSM enrolled in a PrEP demonstration project in the Netherlands [19]. An additional concern is that during follow-up in PrEP studies in France and the Netherlands, HCV incidence rates of about 1/100 person-years for primary HCV infection [20,43] and 25/100 person-years for reinfection were found [43], comparable to incidence rates for HIV-positive MSM. Acute HCV infections in MSM using PrEP have also been reported in the United States and United Kingdom [17,18].

2.1.2 | Molecular epidemiology

Molecular epidemiology is increasingly used to identify clusters and transmission pathways in rapidly evolving pathogens such as HIV and HCV. The main aim of these molecular approaches was to aid the public health response by identifying factors of the epidemic, such as hotspots or emerging clusters, otherwise missed.

Molecular epidemiology has revealed several important aspects of the complexity of HCV transmission networks since the first reports on sexually transmitted HCV infections were published in the mid-2000s. Phylogenetic analyses of HCV sequences derived from HIV-positive MSM in England, the Netherlands, Germany, France [23,44], Australia [45] and the USA [46] between 2002 and 2009 revealed the international connectedness of transmission networks. Molecular approaches also demonstrate the overlap of MSM and PWID clusters in Australia, suggesting the existence of social networks in which both injection drug use and sexual risk behaviours are present [47]. The opposite has also been observed: no overlap of MSM and PWID was observed in the Netherlands when comparing genotype 4 infections [48]. Hence, geographically distinct clustering patterns exist. Transmission clusters of genotypes 1a, 1b, 3a and 4d in MSM have been described globally and represent the major circulating variants, although regional differences exist. In Australia, genotype 1 and 3 are overrepresented among MSM, whereas in the United States subtypes 1a and 1b are more prevalent [40]. Subtypes 1a and 4d cause the majority of infections among MSM in western Europe [12,23], whereas in Asia, subtype 1b and 3a are more prevalent [23,49,50]. Moreover, subtype distribution may even vary by country.

Molecular sequence analyses have demonstrated that HIV-negative MSM on PrEP or eligible for PrEP in the Netherlands and France are infected with HCV strains circulating among HIV-positive MSM [19,43]. Transmission from HIV-positive to HIV-negative MSM seems to occur [19,21]. It is difficult to determine precisely to what extent this transmission occurs via injecting drug use, sexual transmission, or other risk factors, but it seems unlikely that injecting drug use is responsible for a majority of the transmission events in HIV-negative MSM; of the HCV-positive MSM using PrEP in the Amsterdam PrEP cohort, only 23.5% (4/18) reported injecting drug use [19], but in France this was 83% (5/6) [21]. However, numbers in both studies were small. Furthermore, declaring injecting drug use does not equate to sharing injection equipment. Viral sequences collected in Australia and New Zealand suggest that HCV transmission occurs through discrete networks, particularly among HIV and HCV co-infected individuals [51]. In this study, three distinct risk profiles based on the molecular analysis were described: PWID, HIV-positive MSM with low probability of injecting drug use, and MSM with both injecting drug use and sexual risk behaviour. Some clusters with low-probability of injecting drug use contained both HIV-positive and HIV-negative MSM.

These findings suggest that sexual networks of HIV-positive and HIV-negative overlap and that HCV transmission occurs between the two groups. Molecular analyses of already collected HCV strains provide insight in the network complexities of sexual HCV transmission. However, they do not easily translate into actionable public health interventions. Real-time molecular surveillance of these networks may be necessary to eliminate HCV from local MSM communities, especially since high HCV treatment uptake may not be sufficient to lower the HCV incidence in this population, as shown in France [52]. Monitoring of cluster emergence, cluster growth, and cluster characteristics provides a way to identify an outbreak early and the drivers thereof. For HIV, efforts to develop such a system led to HIV-TRACE, a real-time molecular surveillance tool that produces data that can be translated into action [53,54]. Real-time molecular surveillance could aid public health professionals in focusing prevention efforts; an epidemic with new infections that primarily cluster with other locally circulating variants requires a different prevention approach than an epidemic with mostly externally introduced variants. In order to facilitate characterization of external introductions, good regional or global reference sequences are necessary, and testing in combination with active data sharing of HCV sequences is needed. Lastly, network variables that may correlate with cluster emergence/growth (e.g. venue of meeting sexual partners, belonging to specific subcultures) [55,56] should be collected prospectively to target specific prevention measures.

2.1.3 | *Risk factors for acquiring sexually transmitted HCV*

Evidence on risk factors for acute HCV infection is largely based on studies among HIV-positive MSM evaluating determinants of primary HCV infection. Although study design, statistical approach and data collection on potential risk factors differ across studies, these studies have consistently shown that in multivariable analyses incident or acute HCV infection is associated with high risk sexual behaviour, including receptive condomless anal intercourse, unprotected fisting, sharing of toys, chemsex and group sex [10,31,57-60]. Also, the association with recent STIs supports a sexual route of HCV transmission [13,58,60-64]. In addition, a recent study from Canada concluded that all but one HCV reinfection in MSM appeared to have been sexually transmitted [29] and the few studies that restricted behavioural risk factor analysis to MSM who denied injecting drug use, demonstrated risks of sexual transmission of HCV [8,65]. However, there is also evidence for blood-to-blood routes of HCV transmission: injecting drug use, which is reported by a minority of HCV-positive MSM in several studies, sharing snorting drug equipment (straws) and rectal bleeding are associated with an increased risk of incident HCV infection [57,58,60,66-68]. Furthermore, younger MSM, peaking at around age 35, are at increased risk of incident HCV infection [24,62].

Finally, studies consistently show that biological factors might play a role: confection with STI, HIV-1 infection in itself, a lower CD4 cell count and higher HIV RNA levels are associated with an increased risk of incident HCV infection [24,58,66,68]. These factors might affect the mucosal microenvironment and activate specific immune cells within mucosal tissues, which would allow HCV entry and retention.

2.2 | Dendritic cells in sexual transmission of HCV

HCV coinfections with other STIs such as HIV-1, Herpes Simplex Virus type 2 (HSV-2), Chlamydia, Human Papillomavirus (HPV), gonorrhoea and syphilis are common [69-71], suggesting that STIs might directly affect the increased susceptibility to HCV upon sexual contact. Dendritic cell (DC) subsets play an important role in sexual transmission of viruses such as HIV-1 and HCV across mucosal tissues [72,73]. DCs patrol the mucosal tissues to capture invading pathogens for antigen presentation to T cells in the lymph nodes [74]. Anal intercourse is the primary route for HIV-1 infection among MSM

individuals [75], underscoring the importance of the anal mucosa as entry site for sexually transmitted viruses. Langerhans cells (LCs), a mucosal DC subset, have been identified in human sigmoid colon, rectal mucosal tissues [76] and anal tissue of MSM [73,77-79]. Also, HCV is shed into the rectum of MSM with HCV infection [80]. Therefore, LCs could be among the first cells that encounter HCV upon sexual contact. Recently, it has been shown that immature LCs do not transmit HCV but activation of LCs changes this protective behaviour and allows for HCV dissemination to hepatocytes (Figure 1) [73]. HIV-1 infection or activation alters the ability of LCs to efficiently capture and retain infectious HCV either for transmission or to receptive cells for HCV viral egress into the bloodstream (Figure 1) [73]. Also, plasmacytoid DCs (pDCs) are able to sense HCV to receptive cells resulting in antiviral type I interferon (IFN) production by pDCs [81], therefore inhibiting viral spread without becoming infected themselves [82]. Both LCs and submucosal DCs migrate to lymph nodes. The migration of DCs to the lymph nodes might allow transmission of HCV to T cells, as HCV RNA has been detected in peripheral blood mononuclear cells [83-86].

Various receptors have been identified on different DC subsets that are efficient in virus capture, infection and transmission [87,88]. The C-type lectin receptors (CLRs) DC-SIGN and L-SIGN recognize high-mannose N-glycans expressed by different viruses and viral glycoproteins to promote capture of the virus through their carbohydrate recognition domain [89,90]. Both DC-SIGN and L-SIGN interact with HCV glycoproteins expressed by pseudotyped HCV particles or HCV present in sera of infected individuals [88,91]. Co-culture of HCV-treated cells with human liver cells leads to virus transmission to the susceptible liver cells *in vitro* [92,93]. Thus, DC-SIGN and L-SIGN mediate HCV transmission and moreover, capture by these CLRs protects the virus from degradation [94], which could further enhance HCV dissemination. L-SIGN is expressed by liver sinusoidal endothelial cells and could therefore facilitate egress from blood into the liver [88]. DC-SIGN is expressed by submucosal DCs and could be involved in sexual transmission of HCV. Notably, single nucleotide polymorphisms in DC-SIGN that reduce DC-SIGN expression were shown to be associated with a reduced risk of acquiring HCV sexually within a MSM cohort [95]. Upon activation, LCs might upregulate other attachment receptors that facilitate capture and transmission. Cell membrane HSPG, called Syndecans have shown to be important in HCV infection of hepatocytes [96]. The interplay of attachment receptors might be important in allowing HCV entry into mucosal tissues and further dissemination of HCV to the liver. Thus, HCV might hijack DC subsets for transmission and important determinants are HIV-1 exposure and/or immune activation by other STIs. Novel therapies targeting HCV interaction with DC subsets and abrogation of DC activation by HIV-1 or other STIs might prevent HCV transmission.

2.3 | Prevention and the treatment potential

Currently, there is no vaccine to prevent HCV infection. However, the recent availability of DAA for the treatment of chronic HCV with cures rates over 95% [97] has created optimism towards HCV elimination. In many countries treatment is now available for all individuals with a chronic HCV infection, irrespective of fibrosis stage [98]. Modelling studies were the first to demonstrate that rapid scale-up of DAA might limit onward transmission and chronic HCV prevalence and incidence among MSM could decline [99-101]. However, for substantial reductions a decline in risk behaviour is needed as the scale-up of DAA is counterbalanced by ongoing risk behaviour, resulting in initial and reinfections [99-101]. In addition, early treatment, including treatment of acute infection, might further reduce HCV incidence [101,102]. As treatment is costly and treatment uptake varies considerably across countries [103], effective behavioural interventions for MSM at risk of (re-)infection are urgently needed. Qualitative research among HIV-positive MSM with a cured HCV infection in the pre-DAA era showed that the strongest motive to implement risk reduction strategies was the reward of avoiding HCV retreatment and its side effects [104], but this may have changed with the less burdensome DAA treatment. Also sexual risk norms within the MSM population, HCV stigma and non-disclosure of HCV status forms barriers to safer sex, and drug use directly impedes the self-efficacy of MSM to take risk reduction measures [104].

Recently, several studies evaluating the effect of behavioural and/or testing interventions with prompt treatment, on HCV incidence among HIV-positive MSM have been initiated [104]. "Real-life" settings in the Netherlands and Switzerland showed that high uptake of DAA among HIV-HCV co-infected MSM in clinical care, in Switzerland combined with intensive HCV-RNA screening and behavioural intervention, was followed by a reduction in HCV incidence [64,105]. In Switzerland, intensive HCV-RNA screening combined with behavioural intervention was followed by a reduction in HCV incidence [64,105]. However, in France, despite a comparable DAA uptake and cure rate, incidence of primary HCV infection continued to increase and reinfection incidence did not significantly change [52]. More data from "real-life" settings are needed to clarify the impact of DAA uptake on the epidemic. As HCV is also circulating among HIV-negative MSM with high risk behaviour [19,20,52,106] effective interventions, behavioural counselling and routine HCV testing as part of comprehensive sexual health care are needed, to curb the HCV epidemic, in particular for MSM eligible for or using PrEP. For the larger population of HIV-negative MSM routine screening is not recommended but periodic monitoring of HCV prevalence remains important [107]. Finally, efforts to identify and motivate the relatively small proportion of MSM unaware of their positive HIV-1 status to test should be continued as this group might harbor undiagnosed HCV infections.

2.4 | Diagnosis and testing

A large proportion of acute new HIV infections among MSM is caused by MSM who were themselves recently infected by HIV [108]. However, for sexually transmitted HCV there are no studies yet formally quantifying sources of recent infections. The continuing transmission of HCV among MSM in areas with high treatment uptake [52,64,105] suggests that apart from undiagnosed HCV infections in MSM, recently HCV-infected MSM might disproportionally contribute to onward transmission. For treatment as prevention to succeed, early diagnosis and prompt treatment of any new infection is

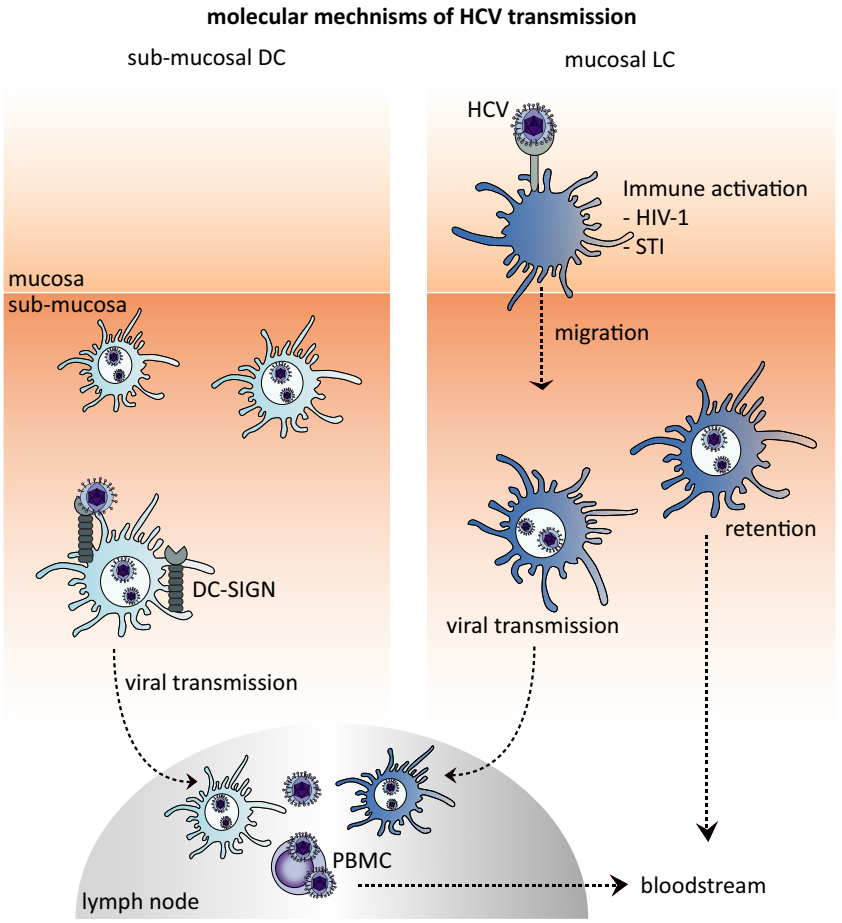

Figure 1. Molecular mechanisms of HCV transmission.
(**A**) Sub-mucosal DCs capture HCV and migrate into the lymphoid tissues to transmit HCV to PBMCs which might lead to further dissemination HCV to the liver. (**B**) Mucosal LCs capture HCV after immune activation by STIs and either retain HCV in the tissue which could increase the chance of virus to egress into the bloodstream and disseminate to the liver or migrate into the lymphoid tissues thereby allowing HCV dissemination to the liver. DC-SIGN, dendritic cell-specific ICAM-grabbing non-integrin; HCV, Hepatitis C virus; HIV-1, Human immunodeficiency virus type 1; PBMC, peripheral blood mononuclear cells; STI, Sexual transmitted infections.

paramount and testing frequency is an important factor in determining success of treatment as prevention [109,110]. Diagnosis of chronic HCV infection includes detection of anti-HCV antibodies, followed by an HCV-RNA test, to distinguish between past and ongoing infection. Diagnosis of acute HCV infection is more challenging as clinical signs and symptoms pointing to acute hepatitis are often absent or aspecific [111]. In addition, HCV-specific antibodies may take a long time to appear: the median time from infection to seroconversion for HCV antibodies is 74 to 91 days in HIV-positive MSM [112,113]. In addition, a minority of patients (less than 5%) remain anti-HCV negative for more than a year [113,114]. Delayed or even absence of seroconversion appears to be caused by HIV-related immunosuppression, as a CD4 + count below 200 cells\μL was associated with seronegative HCV infection [115]. Finally, for diagnosis of acute HCV reinfection, antibody tests cannot be used as after clearance of a primary infection, antibodies may remain present for a long time [112]. Clearly, for diagnosing acute infection early, regular screening, also in asymptomatic patients with a test that directly detects viral RNA or antigen rather than antibodies would be the optimal testing strategy for identifying new cases.

As this comes with a considerable cost, measuring liver enzymes as Alanine Aminotransferase (ALT) level is frequently used as a first step in a diagnostic testing algorithm and has been shown to be more sensitive than testing for anti-HCV antibodies for diagnosing acute HCV infection [113,116]. Although using ALT levels as a first screening step greatly reduces cost as compared to directly detecting HCV RNA, this may result in early acute cases remaining undiagnosed [112,116].

Recently, HCV core antigen has been shown to be a reliable marker for diagnosing HCV infection in chronically infected patients [117]. Regular screening for HCV core antigen may therefore present an attractive strategy for frequent screening of MSM at risk for sexually transmitted HCV. However, reported sensitivity of the core antigen test in a large study with chronically infected patients was 94% when compared with HCV RNA as a gold standard [117]. The reduced sensitivity compared to HCV RNA testing, could result in acute cases remaining undiagnosed, as these

sometimes present with low HCV RNA levels. The few small studies validating the core antigen test for the detection of acute HCV report a sensitivity of 89% to 100% [68,118,119]. Larger studies which include acute HCV cases with a well-documented narrow window of infection are needed before antigen testing can be recommended as a reliable screening strategy for acute HCV infection in routine care.

The cost-effectiveness of HCV screening in MSM could also be increased by focussing on MSM with behaviour facilitating HCV acquisition. Indeed, according to guidelines of the American Association for the Study of Liver Diseases, men with reported high risk behaviour should be offered more frequent HCV testing than the minimal recommended annual testing frequency [109,110]. Risk behaviour can be quantified by using a risk score that is based on risk factors associated with HCV infection. A risk score for identifying acute HCV cases based on six self-reported behavioural risk factors has been developed using data from the MOSAIC study in the Netherlands and appeared to be useful in identifying MSM at high-risk for acute HCV-infection [39]. This risk score was validated using data from three different sources and in these validation studies from Belgium, the UK and the Netherlands, sensitivity ranged from 73% to 100% [39,107]. A risk score could therefore be used as a tool to direct testing resources.

Finally, home-based testing represents an interesting strategy to increase test uptake among high-risk MSM, for example, MSM with a cleared HCV infection, who are at high risk for reinfection. However, currently, only anti-HCV antibody self-tests are available for home-testing, which – as explained above – are not suitable for detecting early acute primary infections or reinfections [120]. Dried blood spots (DBS) collected at home which are sent to a laboratory for HCV RNA testing could be an alternative strategy to facilitate HCV RNA testing. Technically, HCV RNA can be detected on DBS with sufficient sensitivity [121]. The use of home-collected DBS for this purpose remains to be formally validated in terms of technical performance and acceptance by key-populations including key-populations including MSM and PWID. Core-antigen testing on DBS has lower sensitivity and is therefore less suitable for diagnosing acute HCV infection [122].

3 | DISCUSSION

There is growing evidence that HCV is transmitted sexually. In the past decades this epidemic was mostly confined to HIV-positive MSM. However, recent data show that PrEP-using MSM are also at risk for HCV infection, presumably because there is a shared HCV transmission network of HIV-negative and HIV-positive MSM. The association with specific sexual practices strongly suggests that behaviour plays an important role in the ongoing epidemic among MSM. The use of drugs in a sexual context, especially injecting drugs and snorting drugs, is also a major risk factor. The implementation of biomedical HIV-1 prevention strategies, i.e. PrEP and "U=U" (undetectable is untransmittable), might have reduced condom use, and changed sexual networks. This might result in an expanding HCV epidemic in HIV-negative MSM as HCV is more common in HIV-positive MSM. Hence, routine HCV testing and behavioural counselling should be part of PrEP programmes and the epidemic in the larger population of HIV-negative MSM should be closely monitored. And even though DAAs are very effective, the high rate of reinfections further highlights the need for frequent HCV-RNA testing and providing HCV-risk-reduction counselling to MSM with a history of HCV in clinical care. In addition, research into effective interventions aimed at reducing risk behaviour and preventing reinfection should be prioritized as there is a lack of evidence-based interventions and prevention messages might not be sufficient to reduce risk behaviour. Finally, prompt HCV treatment might also contribute to a decrease in HCV prevalence and incidence, especially when combined with additional interventions as part of comprehensive sexual health services.

Factors such as receptive condomless anal intercourse, immune activation by STIs and high-risk sexual practices (e.g. fisting) might increase susceptibility to HCV and could potentially damage the mucosal tissue and cause rectal bleeding, which would facilitate HCV infection [57,60,123,124]. Besides mucosal damage, the activation of mucosal LCs might also allow HCV to enter mucosal tissues and dissemination. HIV-1 infection is a major risk factor in HCV susceptibility, partly because lower CD4 counts but also low HIV-1 replication and immune activation might increase susceptibility. Identification of the molecular mechanisms such as the receptors involved in virus attachment might lead to therapies that prevent sexual transmission of HCV.

Early identification of any recent HCV infections and thus frequent testing of MSM reporting risk behaviour is paramount as these might feed onward transmission. Real-time sequence collection combined with molecular phylogenetics and data collection on network characteristics could identify transmission hotspots, characterize transmission clusters, and determine the relative roles of sustained local transmission versus external introductions, all directing public health efforts to restrain the HCV epidemic among MSM.

3.1 | Study limitations

Studies have consistently shown that the incident of acute HCV infections are associated with high risk sexual behaviour. The role of hygienic procedures (e.g. cleaning sex toys) has not been assessed in these studies but would add to our understanding. Also, no direct comparison of testing strategies, that is, comparing ALT, anti-HCV, HCV RNA and core-antigen longitudinally, for diagnosing acute HCV infection in patients with documented seroconversion exists. As a result, recommendations about testing strategies tend to be somewhat imprecise. Moreover, data on HCV incidence in the wider population of HIV-negative MSM are generally scarce as these men are not in routine clinical care in contrast to HIV-1 infected MSM and MSM using PrEP. In addition, risk factors for incident infection in HIV-negative MSM and for reinfection in HIV positive MSM have not been studied extensively. The lack of such data limits our knowledge on the biological factors that are involved in sexual transmission of HCV. Epidemiological studies show that biological factors also play a role in increased risk of HCV infection. Coinfection with

STIs might affect the mucosal microenvironment and immune activation might change the function of mucosal DC subsets. However, in vivo studies are urgently needed to understand the relevance of the immune cells in HCV transmission and to decipher the route from mucosa to liver.

As HCV (re)infection rates might be regional-specific, more data from other parts of the world than Western Europe, North America, and Australia are needed to obtain a more detailed view of the HCV epidemic among MSM. DAAs are highly effective in curing HCV, but more data from "real-life" settings are needed to clarify the impact of DAA uptake on the epidemic.

4 | CONCLUSIONS

It has been established that HCV can be transmitted via sexual contact. The spread of HCV among HIV-positive MSM in the past two decades and the recent finding of HCV infections in HIV-negative MSM eligible or on PrEP, as well as the association with specific sexual practices, strongly suggest that behaviour plays an important role in the ongoing epidemic among MSM.

Drug use in a sexual context and biological factors as coinfection with STI and HIV-1 also seem to play a role in facilitating HCV spread. At mucosal sites, DC subsets might play a role in HCV dissemination. Targeted and combined prevention efforts including effective behavioural interventions and scale-up of HCV testing and treatment are required to halt HCV transmission in MSM. In addition, real-time molecular surveillance could guide and evaluate prevention strategies.

AUTHOR'S AFFILIATIONS

[1]Department of Experimental Immunology, Amsterdam Infection and Immunity Institute, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands; [2]Department of Medical Microbiology, Laboratory of Clinical Virology, Amsterdam Infection and Immunity Institute, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands; [3]Department of Infectious Diseases, Research and Prevention, Public Health Service of Amsterdam, Amsterdam, The Netherlands

COMPETING INTERESTS

All authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

BMN wrote the manuscript, assembled and edited the manuscript. JK wrote the manuscript. JS wrote and edited the manuscript. MP wrote, edited and reviewed the manuscript. TBHG wrote, edited and reviewed the manuscript.

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