Sexually transmitted hepatitis C infection: the new epidemic in MSM?

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Purpose of review
Increasing evidence has emerged for permucosal transmission of hepatitis C amongst HIV-infected MSM.

Recent findings
A rising incidence of acute hepatitis C virus (HCV) in HIV-infected MSM has been observed since 2000 in Europe, Australia, USA and Asia. Transmission appears to occur through the permucosal rather than the more usual parenteral route. Although often multifactorial, permucosal risk factors can be classified as behavioural (sexual practices and mucosally administered drugs) and biological (HIV and sexually transmitted infections). This review will describe the epidemiology of HCV infection in this cohort. Current and future treatment strategies will also be outlined in the context of novel, orally bioavailable, directly acting antiviral therapies.

Summary
An improved understanding of HCV epidemiology will allow implementation of more effective public health interventions to limit onward transmission of HCV.

Keywords
acute hepatitis C, epidemiology, HIV, MSM, treatment

INTRODUCTION

Parenteral transmission remains the principal route of hepatitis C virus (HCV) transmission. However, over the last decade, there is increasing evidence of permucosal (particularly sexual) transmission, identified predominantly in HIV-positive MSM. Approximately 4–5 million of the 170 million people living with HCV are coinfected with HIV. HIV coinfection is associated with accelerated liver disease and decreased responsiveness to interferon-based HCV treatment [1]. This review will detail the epidemiology, transmission and management of permucosally transmitted HCV infection at a time when new orally bioavailable, directly acting antiviral (DAA) drugs are likely to revolutionize HCV management.

DIAGNOSIS OF ACUTE HEPATITIS C VIRUS

Permucosal HCV transmission has been recognized particularly through the identification of risk factors in the context of acute HCV. Definitions for acute hepatitis C (AHC) vary and determination of the cut-off for transition from acute to chronic infection is arbitrary. Acute HCV was defined in HIV-positive individuals at the European AIDS Treatment Network (NEAT) consensus conference as positive anti-HCV immunoglobulin G (IgG) in the presence or absence of a positive HCV RNA and a documented negative anti-HCV IgG in the previous 12 months; or positive serum/plasma HCV RNA and a documented negative HCV RNA and negative anti-HCV IgG in the previous 12 months. It can also be an acute hepatitis in which other causes have been excluded in the context of appropriate exposure [2▪▪]. In one prospectively recruited cohort of HIV-positive MSM, 77.5% (62 individuals) were identified with AHC due to abnormal alanine aminotransferase (ALT) compared with only 21.2% (17 individuals) through systematic anti-HCV IgG screening [3]. NEAT guidelines recommend

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KEY POINTS

- An increase is observed in permucosally transmitted HCV in HIV-positive MSM in industrialized countries since 2000.
- Risk for AHC transmission is multifactorial: behavioural (sexual practices and mucosally administered drugs) and biological (HIV and STIs).
- Advent of new DAA drugs will significantly improve treatment strategies.

6-monthly screening in HIV-infected MSM at risk for HCV with ALT and annual anti-HCV IgG. For those with a newly diagnosed sexually transmitted infection (STI) or ongoing IDU, screening 3 months after diagnosis/exposure is also recommended. For those with suspected AHC infection, screening with HCV RNA is advised [2▪▪]. Early identification of HCV infection will improve management and may facilitate interventions to limit transmission.

EPIDEMIOLOGY OF SEXUALLY TRANSMITTED HEPATITIS C VIRUS

HCV is most efficiently transmitted parenterally, and, globally, IDUs who share needles and other equipment remain most at risk of HCV [4]. Sexual transmission of HCV in the general population remains controversial and barrier contraception is not supported in international guidelines [5]. In monogamous, heterosexual, anti-HCV discordant couples, low rates of transmission have been identified. In one prospective cohort study of 895 couples with 8060 person-years of follow up, only three transmissions were identified (incidence rate 0.37/1000 person-years), and molecular sequencing demonstrated that the transmissions were probably not sexual [6]. Heterosexual transmission of HCV in this context is estimated to occur at a rate of 0–0.6% per year [6–9] but is higher for heterosexuals with multiple partners or in the context of coexistent STI (0.4–1.8% per year) [10]. As multiple risk factors for acquisition of HCV often coexist in any one at-risk individual, identifying sexual transmissions remains problematic. Furthermore, undisclosed parenteral and household transmission routes may be significant in many contexts [5].

Anti-HCV prevalence was reported as higher (0–23%) in MSM than in blood donors and heterosexuals at risk for STI in early cross-sectional studies [11]. Where information was included on IDU, anti-HCV prevalence was reported as 1–7% for MSM denying IDU versus 25–50% for MSM with a history of IDU [12–15]. More recently, overall European prevalence of anti-HCV antibody or HCV RNA positivity was reported in the EuroSIDA cohort as 33% in the HIV-positive population, varying from 6.6% in MSM to 75% in those with IDU exposure [16]. In the UK, prevalence of anti-HCV antibody in the National Collaborative HIV Cohort (UK CHIC) was 7.2% in MSM [17]. In HIV-negative MSM, HCV seroprevalence remains low and comparable to that of the general population [18–21]. In a recent retrospective UK analysis, MSM with a history of IDU (MSM-IDUs) (97% HIV-negative) were 1.34 times more likely [95% confidence interval (CI) 1.1–1.8] than men with a history of IDU who exclusively have sex with women (MSW-IDUs) to be HCV seropositive and were four times more likely to have unprotected sex with multiple partners than MSW-IDUs [22].

In 2004–2005, a significant increase in the incidence of HCV was reported in HIV-positive MSM in Europe, followed by reports from the USA, Australia and Asia [23–31]. A rising prevalence of HCV was noted in the Netherlands in HIV-infected MSM, which increased from an estimated 1–4% before 2000 to 21% in 2008, with only 5% reporting IDU [18]. High rates of HCV acquisition in MSM with primary HIV infection were also observed in the UK [32]. The characteristics of HIV-positive MSM with permucosally acquired HCV are often similar: urban-centred, aged in their 30s/40s with well controlled HIV, and in most cases denying a history of IDU [5,32–35]. In most of these reported cohorts (excepting Australia), reported IDU was low. In 12 cohorts including 3014 HIV-positive MSM (Concerted Action on SeroConversion to AIDS and Death in Europe), incidence was estimated from 1990 to 2007 using standard incidence methods and methods for interval-censored data. Depending on the analysis used, incidence rose from 0.9–2.2/1000 person-years in 1990 to 23.4–51.1/1000 person-years in 2007, with the main expansion occurring after 2002 [35]. A prospectively recruited Taiwanese cohort of 892 HIV-positive individuals with no history of IDU (731 MSM) reported an overall incidence rate of 7.0/1000 person-years increasing from 0 in 1994–2000 to 2.29 in 2001–2005 to 10.1/1000 person-years in 2006–2010 [31]. A small French study [3] of 80 prospectively recruited HIV-positive MSM estimated lower incidence rates of 4.8/1000 person-years in 2006 and 3.6/1000 person-years in 2007. In the United States, amongst 1830 HIV-infected men enrolled in HIV therapeutic trials 1996–2008, incidence of HCV infection in those denying IDU was 0.4/100 person-years (assumption of predominantly MSM, although data not gathered) versus 2.67/100 person-years in those reporting IDU [36]. A very recent analysis of the Swiss

cohort of HIV-infected MSM with 23 707 person-years of follow up showed an 18-fold increase in incidence rates from 0.23 (95% CI 0.08–0.54)/100 person-years in 1998 to 4.09 (95% CI 2.57–6.18) in 2011. Corresponding incidence rates in the IDU cohort decreased from 13.89 (95% CI 8.20–22.39)/100 person-years to 2.24 (95% CI 0.56–10.66) [37▪]. Incidence rates in HIV-negative MSM seem to remain low, although there may be some degree of underascertainment, as this group is less likely to undergo regular testing. One study [38] from Brighton, UK, reported increasing incidence rates in permucosally acquired HCV in MSM with unknown or negative HIV status, from 0 to 5.8/1000 person-years from 2000 to 2006. However, some of these were subsequently diagnosed HIV-positive, which may partially explain the observed results. In addition, the findings were not replicated in a subsequent study in the same region [39] or in analyses elsewhere. The Australian Trial in Acute Hepatitis C (ATAHC) showed a prevalence in HIV-negative MSM of 1.07%, equal to the general population and 10 times lower than the rate in HIV-positive MSM, although with few transmissions noted in either group [20]. The strongest association with HCV seropositivity in both cohorts was IDU. In more recent data from ATAHC, 25 out of 163 individuals with AHC were men considered to have sexually acquired infection, of which only two (8%) were HIV negative [34].

A further characteristic of the current outbreak in MSM is the alarming number of reinfections reported. In Amsterdam, 11 out of 56 HIV-infected MSM with sexually acquired AHC were reinfected after achieving a sustained virological response (SVR) posttreatment, with a cumulative incidence of 33% within 2 years [40]. A similar trend has been reported in the French HEPAIG cohort, with five out of 80 MSM demonstrating reinfection [3].

Phylogenetic comparison of HCV genome homology has provided further insights into the recent epidemic of HCV in HIV-positive MSM. Robust monophyletic transmission clusters have been identified within the MSM populations of urban centres in the UK, France, the Netherlands, Germany, Australia and Asia [12,31,34,41–43]. An international collaborative study confirmed a large Europe-wide MSM-specific transmission network, which was separate from networks associated with non-MSM IDU transmission [44]. Genetic divergence studies [12,18,45] of these strains suggest multiple independent introductions of HCV into the MSM community since the 1980s, most likely from the IDU population. The notion of multiple strains introduced at different time points supports the theory that changes in MSM behaviour rather than increasing pathogen virulence drove the recent MSM epidemic of HCV. Molecular clock analysis of the sequences [34,44,46] supports the theory that the expansion in these MSM strains increased after 1996, when combination antiretroviral therapy (cART) became widely available, associated with increasing high-risk sexual behaviours [47]. This was also replicated in a USA study [48]. There is also evidence from ATAHC that clusters of AHC in HIV-infected MSM may arise from social mixing of individuals with both IDU and sexual exposures [34].

TRANSMISSION

Parenteral or permucosal transmission of HCV occurs after exposure to infected fluid via a disrupted protective barrier. The majority of permucosal or sexual HCV transmission occurs in HIV-infected individuals. The explanation for the increase in permucosal transmission in this group remains controversial, but key factors can be classified as behavioural and biological. A number of sexual and drug practices associated with mucosal trauma have been associated with transmission. The epidemiological data reveal increasing transmission following the introduction of cART, which has had two significant effects: by prolonging life expectancy, the at-risk population has grown; and it has also led to increased high-risk sexual behaviour, including unprotected anal sex, serosorting and drug use during sex. Biologically, HIV and STIs probably play an important role.

Behavioural factors

Increasing evidence for a role of high-risk sex and permucosally administered drug-taking practices in HCV transmission has emerged over recent years.

HIV and other STIs appear to be important cofactors in onward transmission of permucosally acquired HCV.

Seroadaptive behaviour

This is the practice of seeking unprotected anal intercourse with partners who are believed to be of the same HIV serostatus [49]. In HIV-positive individuals, serosorting has resulted in increased risk behaviour such as reduced condom use and increased traumatic sex leading to higher levels of STIs [50,51]. In 6064 MSM followed by the UK Health Protection Agency from 1998 to 2008, concordant unprotected anal intercourse (UAI) rose from 9.8 to 20.8% [52]. As serosorting with respect to HCV serostatus does not appear to occur, risk of HCV transmission is increased [53].

Mucosally traumatic practices

Three prospective case–control studies have found a correlation between HCV transmission and mucosally traumatic sexual practices. A UK study [41] of 60 cases and 130 controls showed that HCV acquisition was associated with UAI, fisting, rimming, sadomasochistic practices, use of sex toys and group sex on univariate analysis, although only group sex was significant on the multivariate analysis. A German study involving 34 cases and 67 controls identified similar risks, in particular frequent rectal trauma with bleeding, receptive fisting without gloves, group sex and nasally administered drugs. The authors identified rectal bleeding as the key event through which traumatic practices may facilitate transmission [54]. Finally, a US study of 22 cases and 53 controls identified similar risk factors as well as past history of syphilis or gonorrhoea on univariate analysis, although unprotected receptive anal intercourse (URAI) with ejaculation of the partner and nasally administered drugs were significant on multivariate analysis [33]. In a prospectively recruited French cohort of 80 HIV-infected MSM with acute HCV, 90% reported UAI, 65% fisting, 75% seeking sex partners online and 79% at sex venues, and 55% noticed rectal bleeding [3]. In the prospectively recruited MACS cohort (Multicenter AIDS Cohort Study) of MSM, an association between HCV seropositivity and enema use before receptive anal intercourse was reported in the univariate analysis [55]. Similarly, a cross-sectional Dutch study identified an association between enema use before sex and lymphogranuloma venereum (LGV) proctitis in MSM on multivariate analysis. Most participants denied sharing enema tools, and it is possible that enemas facilitate infection through mucosal trauma [56].

Mucosally administered recreational drugs

The extent to which noninjected recreational drugs might directly facilitate HCV transmission versus their effect of disinhibiting sexual behaviour and promoting higher risk sex practices is difficult to disentangle given the high levels of substance use amongst MSM [57]. In addition, underreporting of IDU is an obvious potential confounder. It is, however, biologically plausible that mucosally administered drugs may be associated with permucosal transmission through sharing common instruments, mucosal trauma and mucosal hyperaemia. The UK and German case–control studies identified higher levels of nasally administered drug use in cases [41,54]. In the United States, methamphetamine use during sex was the most significant risk factor for transmission on multivariate analysis in a study of non-IDU, HIV-positive MSM [33]. The most commonly used drugs in these studies included metamphetamine, ketamine, gammahydroxybutyrate, amyl nitrates, 3,4 methylenedioxymethamphetamine and lysergic acid diethylamide.

Biological factors

HIV

HIV may increase both infectiousness of and susceptibility to HCV. HIV increased the serum HCV load by more than 1log IU/ml compared with monoinfected individuals in one cohort [58]. Humoral immune responses to HCV appeared to be attenuated with a delay in development of anti-HCV antibodies, which may be independent of CD4 cell count or likelihood of spontaneous clearance in an observational study of 43 HIV-infected individuals. Approximately 5% of individuals remained antibody-negative after 1 year [59]. Cell-mediated immune responses are also attenuated, with HCV-specific peripheral blood lymphocyte responses reduced in frequency, breadth and magnitude, contributing to reduced clearance of infection [60–62].

In chronic HCV infection, HIV-coinfected individuals are more likely than monoinfected counterparts to shed HCV RNA in semen, implying a possible role in sexual transmission [63]. Most semen studies have examined chronic HCV infection, but a recent small study [64] comparing acute and chronic coinfected individuals found no difference in detection rates of seminal HCV RNA.

Sexually transmitted infections

Mucosally ulcerative STIs such as syphilis and LGV could plausibly facilitate HCV permucosal acquisition through disrupting mucosal integrity. The initial case series of HCV in HIV-positive MSM were associated with syphilis and LGV [12,23,25,65]. In the German case–control study, 56% cases versus 31% controls had a history of syphilis, chlamydia or gonorrhoea in the preceding 12 months [54], with similar findings in the UK case–control study [41]. In a US study [33], syphilis and gonorrhoea were associated with incident HCV on the univariate, although not multivariate, analysis. Syphilis was also identified in the Taiwanese cohort [31]; in the French cohort, 56% (45/80) reported at least one STI in the preceding 12 months including 34 with syphilis [3]; and the Swiss cohort identified past history of syphilis as a predictor of HCV seroconversion [37▪].

MANAGEMENT

The overall rate of spontaneous clearance of HCV has been estimated at 25% [66]. A proportion of HIV-infected individuals with AHC spontaneously clear the infection (0–40%), although less than in monoinfection (15–50%) [2▪▪,24,42,60,62,67–70]. In prospective studies, 7.2% of HIV-infected MSM developed jaundice [41] compared with 0–68% of HIV-negative individuals exposed via IDU or needlestick injuries [71,72]. Spontaneous clearance in coinfected individuals may be predicted by multiple factors, including higher CD4 cell counts and lower HCV RNA levels [24], high ALT [62], female sex, mode of transmission, HBsAg positivity, region [68], nonblack ethnicity, younger age [73], presence of jaundice and nosocomial transmission [70]. In monoinfection studies, individuals with *IL28B* with CC homozygous genotype demonstrate increased likelihood of spontaneous clearance, as well as treatment responsiveness [74,75], although there are conflicting reports regarding its significance in coinfection [76–78]. Those who clear AHC spontaneously show an early, rapid drop in viraemia. Absence of at least a 2 log10 drop in serum HCV RNA 4 weeks after presentation and persistent viraemia at 12 weeks after presentation are considered indications for treatment [2▪▪]. A short delay following diagnosis (12 weeks) does not appear to compromise interferon-based treatment success [79], whereas a delay of more than 12 months halves SVR rates in HIV-negative individuals [71].

Treatment responses for HCV infection, in general, are considered to be reduced in HIV coinfection. However, interferon-based therapy for AHC is still more effective than in chronic hepatitis C (CHC) in this cohort. In ATAHC, 80% patients receiving therapy with pegylated interferon and ribavirin achieved SVR [80]. The NEAT consensus conference reviewed nine reported cohorts, which included 170 HIV-positive individuals receiving treatment for AHC with predominantly genotypes 1 or 4, and found that most SVR rates were between 60 and 80% compared with 30% for genotype 1 in CHC [2▪▪]. In the European Collaborative Cohort Study of 111 HIV-infected men with AHC, overall SVR was 62%: 93% of those with a rapid virological response (RVR) achieved a SVR, whereas only 9% not achieving complete early virological response reached SVR [69]. The NEAT guidelines in HIV-infected individuals therefore recommend that duration of pegylated interferon and ribavirin should be based on RVR: individuals with an RVR should receive 24 weeks of therapy and those with no RVR should receive 48 weeks. If there is less than a 2 log10 drop in HCV RNA at 12 weeks, treatment should be discontinued [2▪▪].

The advent of DAA drugs is likely to revolutionize HCV management, with the potential for once-daily dosing oral regimens, short duration courses (6–24 weeks), enhanced tolerability and remarkably high efficacy (>90% cure rates). HCV viral protease (NS3/4A) inhibitors prevent posttranslational processing of the HCV polyprotein. Currently licensed drugs in chronic infection with genotype 1 are telaprevir and boceprevir. These have improved 24-week SVR rates in treatment-experienced patients with chronic HCV monoinfection from 38–44% to 66–75% and enabled shorter treatment durations [81–83]. However, they are both given with pegylated interferon and ribavarin, and therefore toxicity rates are high. Several small studies have also shown improved SVR rates in HIV-infected patients with chronic HCV [84,85]. Their use may be complicated by multiple pharmacological interactions between antiretrovirals and both telaprevir and boceprevir [86].

Novel strategies are likely to employ interferon-free regimens with many small molecular DAAs currently in phase 2 and 3 clinical trials. Some of the DAAs, such as nucleos(t)ide analogues, have cross-genotype activity, a high genetic barrier to resistance and lack the cytochrome P450 3A4 interactions associated with the HCV protease inhibitor class and may therefore be particularly attractive for patients receiving antiretrovirals [87].

CONCLUSION

Increasing evidence has accumulated from cohort and case–control studies characterizing an epidemic of HCV in HIV-positive MSM in high-income countries, transmitted permucosally. Cumulative incidence appears to be increasing, and new outbreaks, for example in Taiwan, have been recently described. Monophyletic MSM-specific strains of HCV, mostly with difficult-to-treat genotypes 1 and 4, have been observed and appear distinct from strains isolated in heterosexuals with IDU exposure. Separate phylogenetic networks have been identified in Europe, Australia and the USA, implying that MSM-specific networks have arisen *de novo* in each of these regions. High-risk sexual and drug-taking practices have been observed, likely due to changes in sexual behaviour since the widespread deployment of cART. HIV is also likely to be an important factor in transmission, and it is notable that amongst HIV-negative MSM, few cases of permucosally acquired HCV have been observed. Management of HCV in this group will change significantly with the advent of DAAs and the likelihood of short course, orally bioavailable treatment regimens. Although most studies have focused on

CHC, the benefit for patients with AHC will likely follow. However, as HCV treatment becomes increasingly tolerable and efficacious, it is possible that this may herald not only a leap forward in HCV management but also a substantial increase in risk-taking behaviour and transmission of HCV, repeating what has been observed following the widespread use of cART for HIV. Similarly, the promising results of treatment as prevention studies for HIV may drive interest in pursuing this strategy with DAAs to combat HCV transmissions in the future [88].

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Conflicts of interest

There are no conflicts of interest.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 102).

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