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CO-INFECTIONS AND COMORBIDITY (S NAGGIE, SECTION EDITOR)

# Acute HCV in HIV-Infected MSM: Modes of Acquisition, Liver Fibrosis, and Treatment

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**Abstract** Hepatitis C virus (HCV) is not considered to be efficiently transmitted sexually, but since the early 2000s, HCV infection of HIV-infected men who have sex with men has emerged as an epidemic worldwide. In this review, we discuss the epidemiology of sexually transmitted acute HCV, the growing body of literature regarding risk factors for acquisition, and possible mechanisms of transmission. We also discuss the progression of liver disease in these men and the advances in therapy of acute HCV with interferon-free regimens and put forth our current approach of evaluating and treating these men in New York City.

**Keywords** Acute hepatitis C (HCV) infection · Sexual transmission · Men who have sex with men (MSM) · HIV/AIDS · Direct-acting antivirals (DAA) · Liver fibrosis

## Introduction

Hepatitis C virus (HCV) is not considered to be efficiently transmitted sexually; blood exposure, particularly through injection drug use (IDU) and needle sharing, is responsible for the overwhelming majority of hepatitis C virus (HCV) infection worldwide [1]. Just over a decade ago, however, the first reports appeared from Europe [2–6], Australia [7], and the

USA [8, 9] of an emerging epidemic of acute HCV infections in HIV-infected men who have sex with men (MSM) who did not engage in IDU. Over the ensuing decade, rates of HCV infection have continued to increase in these men.

The purpose of this review will be to describe the emerging and recent literature on the diagnosis, risk factors, and mechanisms for acquisition, liver fibrosis during, and management of acute HCV infection among HIV-infected MSM.

## Diagnosis of Acute HCV in HIV-Infected MSM

Acute HCV can be defined functionally as the period after infection during which spontaneous clearance may occur and in which less intensive interferon-based therapy is more effective compared to chronic HCV infection. Some have also suggested that acute phase lasts the first 6 months of infection [10], although the variability due to diverse host as well as viral characteristics is wide. There is, therefore, no single accepted definition of acute HCV infection, as its characteristics are not fully defined.

Antibody (Ab) screening is usually considered the mainstay of the diagnosis of chronic HCV. In HIV-uninfected people, the time from HCV infection to seroconversion is about 6 weeks, ranging up to 10 weeks with third-generation testing [11]. Thomson et al. [12] suggested HIV-infected men had a longer time to seroconversion, with a median of 91 days, and 4 out of 43 did not seroconvert in the observed time of up to 218 days follow-up in a cohort in London. Subsequently, Vanhommerig et al. have performed a careful follow-up study in their cohort of HIV-infected MSM with acute HCV infection in Amsterdam using stored plasma samples from 66 patients [13••]. They found a median time to seroconversion of 74 days, which they considered to be within the range of the expected time to seroconversion of HIV-uninfected people,

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although clearly on the upper end of the range. Ninety-eight percent of men had seroconverted within 1 year and all seroconverted during the observation period. They further showed a remarkably high sero-reversion rate of 8 (37 %) of 31 men who were cured by interferon treatment. Interestingly, Ab levels rebounded fully in those who were reinfected.

In new guidelines released in June 2015, the CDC have recommended an increase over previous recommendations in the degree of surveillance for incident HCV, through more frequent HCV Ab testing of sexually active HIV-infected MSM [14]. Alanine aminotransferase (ALT) testing, however, is more sensitive than Ab testing, especially when using the correct upper limit of normal for men of 30 IU/mL [15]. After incident HCV infection, viremia is detectable within a week and ALT becomes elevated in 4 weeks, which is weeks to months before Ab production [12, 13••]. Since our goal is to treat HCV in the acute phase, an early diagnosis is needed. Our screening practice is therefore to perform quarterly ALT testing followed by confirmatory HCV RNA testing for any new ALT elevation in HIV-infected MSM at high risk for HCV. In this setting, HCV Ab seroconversion is a useful additional confirmatory test, and therefore, annual HCV Ab testing is helpful to maintain a baseline. Using HCV Ab as a screening test is the least useful when patients present with a symptomatic sexually transmitted infection (STI) or after exposure to STI, as HCV Ab would be still negative. Under these circumstances, screening with HCV RNA testing and ALT is more accurate, and HCV Ab testing is done only with the goal of establishing a new baseline. As with any STI, after exposure to or symptoms of one, comprehensive testing for others (GC, CT, syphilis) should be undertaken as well. Finally, the need to follow up any elevation in ALT with HCV RNA testing [16, 17] in HIV-infected MSM must be stressed, as the initial HCV presentation can be of only low-level ALT elevation. HCV antigen assays are currently under investigation and have shown excellent sensitivity [18]; however, none are commercially available in the USA at this time.

## Epidemiology

Since the first reports of sexual transmission of HCV among HIV-infected MSM from Northern Europe [2, 3], numerous reports have been published from cohorts in almost every Western European country, as well as Australia and the USA. Studies of incident HCV in Amsterdam [19], Belgium [4], and Switzerland [20] found increasing rates through the first decade of the twenty-first century. Two large HIV cohorts in Asia have now reported similar findings, expanding the evidence of this epidemic to another continent. In Taiwan, 30 HIV-infected men, 28 of whom were MSM, seroconverted between 1994 and 2010. HCV incidence increased from zero between 1994 and 2000 to 12.3 per 1000 person-years (PY)

between 2006 and 2010 [21]. In Tokyo, 21 HIV-infected patients, 17 of whom were MSM and did not inject drugs seroconverted between 2005 and 2012. The incidence increased from zero between 2005 and 2006 to 20.2 per 1000 PY between 2011 and 2012 ($p$=0.045) [22]. Ishikane et al. [23] from the same Tokyo institution, reported 35 men with acute HCV, at least 31 of whom were MSM, in the period between 2001 and 2012 (2.1 cases per 1000 PY overall).

In follow-up of earlier work in Amsterdam, two recent reports suggest that the Amsterdam epidemic has stabilized since approximately 2005 to 2008. Urbanus et al. performed HCV Ab testing on anonymous blood specimens collected at a central STI outpatient clinic and found a stable prevalence between 2008 and 2010 after having increased since 1995 [24••]. With this finding, Vanhommerig et al. [25] analyzed the newest data from the Amsterdam cohort study and found a similar plateau in incident cases among HIV-infected MSM after approximately 2005, although based on just 26 incident cases since 2000. One limitation of these data, however, is they do not capture reinfections. A contemporaneous study from another institution in Amsterdam reported a reinfection rate after cure or spontaneous clearance of over 15 % [26], and Vanhommerig et al. [13••] from a different cohort reported 18 reinfections out of 31 HIV-infected MSM in Amsterdam who were cured or spontaneously cleared, suggesting a true incidence rate in Amsterdam that is higher than those determined by seroconversion. Reinfection rates have been high not only in Amsterdam but also in Germany and New York City [27••]. Ingiliz et al. recently published high rates of reinfection among German MSM, with 11 of 48 HIV-infected MSM experiencing their third HCV episode [28•].

The epidemic in the USA has been more difficult to quantify, with most regional cohorts unable to provide incidence rates [8, 9, 29–31, 32•]. There have been two studies with national sampling, however, that have been able to estimate incidence. In a sampling of active participants in ACTG randomized trials, Taylor et al. found 27 incident infections among HIV-infected MSM for an incidence rate of 5.1 per 1000 PY [33]. A four-center cohort of MSM, the Multicenter AIDS Cohort study (MACS), found a total of 115 cases of incident HCV in HIV-infected MSM over the period from 1984 to 2011, for an overall incidence of 2.1 per 1000 PY, which was stable over the study period [34•]. In New York City (NYC), in contrast, in addition to the 74 cases of sexually acquired acute HCV among HIV-infected MSM we reported from our single study site between late 2005 and 2010 [30], we have seen approximately 100 cases more since then [Fierer, unpublished data]; since these were referred cases, we are not able to calculate an incidence rate. The NYC Department of Health, however, has just published the first population study in this field, which shows the magnitude of the problem in NYC. Through mandatory laboratory reporting data for both HIV and HCV, Breskin et al. identified almost

42,000 HIV-infected MSM in NYC diagnosed before 2010 whose HIV was acquired through sex with men, excluding IDU, and who did not have laboratory diagnosis of HCV within 3 months of HIV infection. In the period between 2000 and 2011, they found an impressive 2016 incident cases of HCV [35••]. The overall incidence of 6.0 per 1000 PY was not stratified by time over the first decade of 2000 but is the upper range of the other American as well as European and Asian cohorts [36].

## Risk Factors for HCV Acquisition

Four initial high-quality case-controlled studies from four countries [20, 30, 37, 38] reported apparently different and difficult-to-reconcile sets of risk factors for acquiring HCV infection. More recently, two additional high-quality studies have been published that not only help clarify the actual risks but also help to reconcile the previously discordant reports of HCV acquisition among HIV-infected MSM (Fig. 1).

In a case-controlled study from the USA, Witt et al. reported that incident HCV infection among HIV-infected MSM was mainly associated with unprotected receptive anal intercourse with multiple partners, antecedent syphilis, and history of IDU; older age, moderate alcohol use, hepatitis B

coinfection, and lower CD4 count were also associated but to a lesser degree [34•]. Anal trauma was not reported. In the most recent study, Apers et al. [39•] in Belgium found that douching prior to anal intercourse, a question not asked in other cohorts, was the strongest association with HCV acquisition (AOR 13.5), higher than the other significant risks of fisting, serosorting, or infection with gonorrhea or chlamydia in the year prior. Vaginal douching has been associated with increased risk of HIV [40] and chlamydia [41] infections; thus, it is plausible that anal douching might increase the porousness of the anal mucosa, allowing more efficient transfer of a low inoculum of HCV introduced by semen or a fomite.

HCV infection of HIV-uninfected MSM has been reported only rarely, and this finding holds true in observational cohorts not biased by intensity of screening. While HIV may play a biological role in decreasing the barrier to HCV infection during sex, an additional hypothesis is that HIV is much more infectious through sex, resulting in HIV infection preceding HCV infection in men who are exposed to both viruses. With the practice of serosorting without condom use [42], HCV would therefore be concentrated in HIV-infected men. Proof in principle of this latter hypothesis is the very recent report from Kaiser of northern California [43•] that described two men who were taking pre-exposure prophylaxis (PrEP) but not using a condom who acquired HCV infection. We had
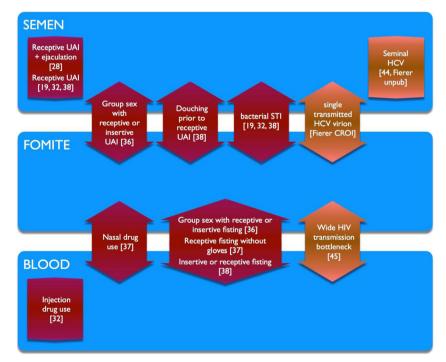


**Fig. 1** Model for modes of HCV acquisition/transmission by HIV-infected MSM during sex. Findings from multivariable analyses of five published case-control studies of HIV-infected MSM with acute HCV are represented by *darker, maroon-hued icons*. Findings from molecular studies investigating HCV transmission are represented by *lighter mocha-hued icons* to the *right side* of the figure. *Squared icons* placed entirely within the *horizontal bar* representing a single transmission mode represent evidence suggesting only a single mode of acquisition/transmission. *Double arrowhead-shaped icons* that straddle two *horizontal icons* represent the possibility of the risk factor contributing to two modes of acquisition/transmission. Similar risk factors from different studies are grouped within a single icon. References are in *square brackets*

concurrently made the same observation in three men newly taking PrEP who acquired HCV (and not HIV) in NYC [Fierer, unpublished observations]. These cases strongly suggest that the reason we see so few HIV-uninfected MSM with acute HCV is not as much that surveillance in HIV-uninfected men is poor or that the rectal mucosa of HIV-uninfected men is less porous to HCV in the absence of HIV infection, but is largely stochastic, that HIV is more infectious than HCV through sex, unless the HIV infection is prevented by PrEP. We suggest, therefore, that all MSM prescribed PrEP be warned that HCV is an additional infection (to the traditional STI) that can be acquired if condoms are not used and that the quarterly lab surveillance be with a comprehensive metabolic panel rather than just a basic metabolic panel, along with at least annual HCV Ab testing.

## Mechanisms of HCV Transmission During Sex

Epidemiological studies have implicated semen as a likely body fluid transmitting HCV to the receptive partner during unprotected receptive anal intercourse [30]. Additionally, HCV has been demonstrated in semen of both HIV-uninfected [44] and HIV-infected [45, 46] men during chronic HCV, although HCV was not detected in every semen sample and when present was at low levels compared to blood. One study found nominally higher seminal RNA in men with HIV infection [46]. Seminal HIV RNA is much higher during acute HIV infection, leading Bradshaw et al. [47••] to measure HCV seminal RNA during acute HCV. The study compared paired blood and semen samples in HIV-infected men with acute and chronic HCV infection. They found lower rather than higher seminal HCV RNA during acute HCV, correlating with the lower blood RNA during acute HCV. We performed a similar study with very similar results [Fierer, manuscript in preparation]. Both studies found an apparent threshold affect where seminal HCV was not detected in men with blood RNA levels below 6 $\log_{10}$ IU/mL.

Two recent studies have used molecular techniques developed for understanding HIV transmission and applied them to HCV transmission. Kouyos et al. [48•] demonstrated that men with a wider HIV transmission bottleneck, indicating that a larger number of viruses (also termed transmitter/founder viruses) caused the initial HIV infection, had a threefold higher chance of new HCV infection. The hypothesis proposed by the authors was that a wider HIV transmission bottleneck was indicative of having had sex that resulted in higher HIV inoculum through damaged mucosal barriers. This behavior might then have continued, resulting in the subsequent acquisition of HCV, possibly suggesting a wider HCV transmission bottleneck. We directly investigated the HCV transmission bottleneck by identifying and enumerating the transmitted/founder HCV in 10 new HCV infections in HIV-infected MSM [Fierer

et al., Assessing HCV Acquisition Routes in HIV-infected MSM Using Single Genome Sequencing—A Pilot Study, poster 674, 21st CROI, 2014]. We found that 8 of 10 infections were caused by a single transmitted/founder virus. Among the two with high numbers of transmitted/founder viruses, one had shared injection equipment, the expected finding in this setting, and one had no identifiable risks for the large number of transmitted/founder viruses identified. This overall result of only a single transmitted/founder HCV in men with sexually acquired HCV is very similar to that of sexually acquired HIV and suggests that sexual acquisition of HCV does not require significantly more rectal trauma than sexual acquisition of HIV. The result is also consistent with the transmitting fluid having a low HCV titer, on order of that found in semen, rather than that of blood.

These molecular data taken together with the epidemiological data, lead us to propose that the epidemic of HCV transmission among HIV-infected MSM is comprised of a combination of sexual (i.e., in semen) transmission, fomite transmission, and blood-based transmission (Fig. 1). While bleeding during sex may certainly be sufficient to transmit HCV [38], the available evidence shows that it is not necessary. Susceptibility to HCV may be increased if the rectal mucosa is compromised by douching or by HIV infection itself, with studies showing lower CD4 count is a risk, albeit a weaker association than most. Fisting could cause local trauma but there is no donor virus unless the fist itself bleeds, which is unlikely. Fisting in group settings, however, is likely to result in the fist being a fomite even without rectal bleeding. The penis could also be a fomite in the setting of group sex, again, even without rectal bleeding. Fomite transmission has been demonstrated with *Salmonella*, *Shigella*, hepatitis A, *Giardia*, and lymphogranuloma venereum [49–53] among MSM. Fomite transmission of HCV is consistent with both the epidemiological associations between HCV acquisition and anal intercourse during group sex, fisting with or without group sex, as well as with our transmitted/founder HCV findings (Fig. 1).

## Liver Fibrosis

Liver fibrosis within the first months after acute HCV has been demonstrated in each of the four studies of HIV-infected men in which liver histology was examined [4, 9, 23, 54], with the finding of a rapid onset of stages 2 to 3 (scale 0 to 4, Scheuer classification system) liver fibrosis in most men. Higher stages of fibrosis were found with longer time to biopsy [54], and in some cases, progression to liver failure occurred within a few years of infection [55]. Some have questioned the clinical significance of these biopsy findings, however [56]. To better delineate the mechanism of biopsy findings in these men with acute and recent HCV infection, we reassessed our biopsy specimens for evidence of activation

of the collagen-producing cells in the liver, the hepatic stellate cells. Activation of hepatic stellate cells was significantly greater in biopsies performed within 1 year of HCV diagnosis than in biopsies performed ≥1 year after HCV diagnosis [Fierer DS, Gillies R, Yip MJ-S, Friedman S, Branch AD, Dieterich DT, and Fiel MI. Activation of Hepatic Stellate Cells Drives the Rapid Onset of Liver Fibrosis During Acute HCV Infection in HIV-infected Men. Poster 2514 presented at the 20th International AIDS Conference, Melbourne Australia, July 20–25, 2014]. More research with better long-term follow-up is clearly needed to better understand the transition from the early development of fibrosis in most men to serious liver disease in a subset of these men. Based on these available data, however, we propose a model of liver injury in HIV-infected men with acute HCV in which the high-level activation of hepatic stellate cells results in the production of excess collagen and therefore liver fibrosis in the first year after HCV infection. Subsequently, the high-level activation decreases to levels typically found in chronic HCV, which results in the slower but continued progression of fibrosis. Due to the initial burst of fibrosis, although there are limited data on the accuracy of longitudinal noninvasive fibrosis testing, we recommend that any HIV-infected man who does not receive early curative treatment for acute HCV be monitored noninvasively for evidence of advancing liver disease while awaiting optimal treatment. In the USA, where such treatments are available, these men should be treated immediately.

## Treatment: with What, in Whom, and When

Whom, how, and when to treat for acute HCV infection are pressing issues in light of an accelerated course of liver disease as well as risk of continued transmission in persistently viremic men. Direct acting antivirals (DAA) against HCV have resulted in a rapid evolution of treatment regimens for chronic HCV. We have adapted these treatment regimens for acute HCV, cutting in half the treatment duration. We used a short course of 12 weeks of telaprevir (TVR)+peg-IFN+RBV for genotype 1 acute HCV in HIV-infected men, curing 16 (84 %) of 19 men [27•]. Enrollment was subsequently expanded to 38 men, including two with genotype 2 HCV, resulting in a cure rate of 34 (89 %) of 38, compared to 30 (63 %) of 48 men cured in the comparator peg-IFN+RBV group treated for 24+ weeks ($p=0.01$) [Fierer D., unpublished data]. The tolerability of TVR+peg-IFN+RBV was not as good as its efficacy, and almost all had pruritus and were uncomfortable with the fatty meal requirement. Using boceprevir (BOC) for 12 weeks with peg-IFN+RBV (without IFN lead-in), the Dutch DAHHS study results have so far been disappointing, with a cure rate of 78 % [van der Meer J et al., SVR 12 Results after 12w Boceprevir+P/R in the Dutch Acute Hepatitis C in HIV Study. Presented at CROI 2015], which is no better than the 76 % cure rate reported by the Dutch centers using peg-IFN+ RBV without a DAA [57]. BOC is a much slower-acting drug than TVR, which is likely the explanation for its lack of success in the short 12-week acute HCV treatment course. It is of further concern for the usefulness of these first-generation HCV protease inhibitors (PI) that resistance to TVR was transmitted sexually to a partner, causing subsequent failure of therapy with TVR [58•].

With the release of sofosbuvir (SOF), however, it is clear that the interferon era has ended. There are as yet no published data in treating acute HCV with IFN-free regimens but we will discuss the available results from our center. Maintaining our treatment paradigm for acute HCV of halving the treatment duration used for chronic HCV, we treated 11 HIV-infected MSM with acute genotype 1 HCV with 12 weeks SOF+RBV, curing 10 (91 %) of 11 [Fierer, manuscript in preparation]. A larger, multicenter, open-label trial, ACTG 5327, has recently completely enrollment and results are expected by the fall of 2015 [Naggie S and Chung R, personal communication]. However, even if this larger study confirms this high cure rate, RBV has many side effects (even without IFN), and the availability of DAA combinations that do not require RBV is more appealing for acute HCV treatment in the long run. SOF/ ledipasvir (LDV) is therefore an attractive alternative, especially as the epidemic has so far been mostly genotype 1a worldwide, with some genotype 4 virus in Europe. Continuing the model of acute HCV treatments being half the duration of chronic HCV treatments, studies of SOV/LDV are planned to test the effectiveness of 6- and 8-week courses. Demonstrating the effectiveness of 8 or fewer weeks of SOF/LDV in treating acute HCV would be helpful to those concerned about cost of treating early in acute HCV.

The availability of IFN- and RBV-free regimens that are both safe and extremely effective has changed how we think about whom and when to treat. In the interferon era, physicians treating men in this epidemic generally encouraged treatment of all men who were willing, and most of these patients accepted this onerous treatment. European (NEAT) guidelines [59] developed based on peg-IFN+RBV treatment suggested treating all who wished treatment and making the decision of when to treat based on the pattern of spontaneous viral load (VL) fluctuations in the first 4 weeks after HCV diagnosis. In those with a <2-log spontaneous VL drop in this period, they suggested there was no significant chance of spontaneous clearance, and therefore, treatment should be initiated immediately. If there were a >2 log drop in VL, spontaneous clearance might occur, and patients should then be observed for an additional 8 weeks and offered treatment if still viremic at the end of this total of 12 weeks of observation. The duration of peg-IFN+RBV was then to be half that compared to chronic infection. Now in the IFN-free era, the

AASLD/IDSA guidelines [60] have taken a more conservative approach, not directly recommending treatment of all HIV-infected patients with acute HCV, while further recommending a longer period of delay to allow for spontaneous clearance of 12 to 16 weeks. The treatment would then be as for chronic infection. However, spontaneous clearance is rare (15 %) in these HIV-infected MSM [reviewed in 27]. While during the IFN era, the medical reason to delay treatment was to allow for even this relatively small chance to avoid the significant toxicities of IFN and RBV (even worse with TVR and BOC), that medical reason is no longer applicable in the post-IFN era. The evolution in HCV treatment, with more potent and less toxic DAA replacing weaker and less tolerable treatment options, in some ways parallels the evolution of HIV antiretrovirals (ARVs) between the mid-1990s and the late 2000s. With these newer ARVs, we now recommend treating HIV immediately after diagnosis, both for the health of the individual being treated and for the health of the community in decreasing transmission. The justification is the same for HCV.

We therefore suggest that we should now treat all HIV-infected patients with acute HCV who wish to be treated as soon as is practicable and eliminate the structured treatment delays that have recently been recommended [59, 60] for the following reasons. First, as stated above, spontaneous clearance is rare in these men, and testing provides poor accuracy to predict who will progress to chronic infection on the individual level [59]. Second, long (i.e., >4 weeks) structured treatment delays can result in waning of the advantage of the enhanced treatment response period resulting in failure of the short-course approach to treatment. This was true with peg-IFN+RBV treatment [61, 62], and it is reasonable to believe it will be the case for the desired short courses of IFN-free DAA combination therapies. Third, as with new HIV infections, most of our patients do not want to delay treatment and prefer to be treated immediately. Not treating them quickly results in disengagement in care and loss to follow-up [61]. Prolonged viremia during the acute phase even without loss to follow-up increases the risk of transmission to other men, propagating the epidemic. Fourth, with rapid development of liver fibrosis in most HIV-infected men after acute HCV [9, 54] and a continued accelerated course of liver disease in a subset [55], some would therefore be medically adversely affected by delay or loss of treatment. Finally, available modeling suggests that delay in treatment after acute infection increases the risk of liver-related mortality and clinical outcomes [Zahnd C et al. Impact of Deferring HCV Treatment on Liver-Related events in HIV+ Patients. Abstract 150. Presented at CROI, 2015]. There are also no studies supporting the cost-effectiveness of the currently recommended structured treatment delays of a DAA regimen. On its face, then, it

appears to be more expensive rather than less expensive (and less acceptable to the patient and to the community) to delay treatment than to prepare to treat immediately.

Our practice, therefore, is to not delay in applying for treatment after initial evaluation results are available. We continue to monitor for spontaneous clearance closely throughout the application process and treat those who do not appear to be clearing during this typically 4- to 8-week period. In patients whom we then judge are still in the period we describe as the "enhanced treatment response" phase of acute HCV, we are currently treating with SOF/LDV for genotypes 1 and 4 for 8 weeks and SOF+RBV for genotypes 2 and 3 for 8 weeks, pending evidence that even shorter courses are equally effective. For those practitioners who are not as comfortable diagnosing and treating acute HCV infection, however, we suggest the AASLD/IDSA recommendation of treating as for chronic infection.

## Conclusions

The worldwide epidemic of sexually transmitted HCV infection among HIV-infected MSM has continued to expand in scope over the last 10 years to four continents in both hemispheres and has become increasingly prevalent in almost all cohorts in which it has been evaluated. It has become clearer through epidemiological and now molecular studies that HCV can likely be transmitted by semen, via fomites, and possibly by blood during sex. We now need to build on these studies to more directly test the possible routes of transmission. Such novel studies are urgently needed to develop more effective prevention strategies as part of a multi-pronged approach to reversing this epidemic of sexually transmitted HCV.

The rapid development of liver fibrosis during acute HCV in HIV-infected men highlights the importance of close follow-up and monitoring of these patients. Fortunately, with the approval of multiple DAA for chronic HCV, we have safe and potent IFN-free combination treatments available to treat acute HCV, but the experience is still too small to define the definitive regimen(s) for the treatment of acute HCV. Clinical trials in acute HCV are needed to determine when to start treatment and how much we can shorten treatment with these potent combination DAA while still achieving cure rates that are as good as the >95 % rates demonstrated with longer treatment courses for chronic HCV. Further, as has now been done with HIV infection, we need to study the approach of treatment as prevention to cure HCV infection as soon as possible to decrease risk of transmission. To get the most from these highly effective therapies, we must also work to prevent reinfection by both engaging patients in care and addressing the sexual behaviors associated with further transmission or reacquisition. Finally, with their high up-front cost, the data from treatment and prevention studies will be essential in

appealing to insurance companies and the offices of Medicare and Medicaid in the USA, and government programs worldwide to pay for these treatments. As fighting for funding of HIV treatment was one of the major advocacy issues faced during the era of AIDS, fighting for funding for HCV treatment will likely be the same for this generation of HIV-infected patients and their healthcare providers.

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