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HCV epidemiology in high-risk groups and the risk of reinfection

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List of abbreviations: PWID, people who inject drugs; MSM, men who have sex with men; HCV, hepatitis C virus; IDU, injecting drug use; DAA, direct-acting antiviral; PY, person-years; NSP, needle/syringe provision; OST, opioid substitution treatment; HIV, human immunodeficiency virus; SVR, sustained virological response; RNA, ribonucleic acid; NGS, next generation sequencing; PCR, polymerase chain reaction.

Key words: HCV; reinfection; epidemiology; PWID; MSM; injecting drug use; risk behaviours.

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Summary

Injecting risk behaviours among people who inject drugs (PWID) and high-risk sexual practices among men who have sex with men (MSM) are important routes of hepatitis C virus (HCV) transmission. Current direct-acting antiviral treatment offers unique opportunities for reductions in HCV-related liver disease burden and epidemic control in high-risk groups, but these prospects could be counteracted by HCV reinfection due to on-going risk behaviours after successful treatment. Based on existing data from small and heterogeneous studies of interferon-based treatment, the incidence of reinfection after sustained virological response range from 2-6/100 PY among PWID to 10-15/100 PY among HIV-infected MSM. These differences mainly reflect heterogeneity in study populations with regards to risk behaviours, but also reflect variations in study designs and applied virological methods. Increasing levels of reinfection are to be expected as we enter the interferon-free treatment era. Individual- and population-level efforts to address and prevent reinfection should therefore be undertaken when providing HCV care for people with on-going risk behaviour. Constructive strategies include acknowledgment without stigma, education and counselling, harm reduction optimization, scaled-up treatment including treatment of injecting networks, post-treatment screening, and rapid retreatment of reinfections.

Key points (1)

- Sharing needle/syringes and contaminated ancillary injecting equipment (spoons/cookers, filters, and water) are the main risk factors for HCV acquisition among PWID
- Risk factors for HCV acquisition among MSM include traumatic sexual practices, mucosally administered and injecting recreational drug use, HIV infection, and ulcerative sexually transmitted infections
- Combined harm reduction interventions (needle/syringe provision and opioid substitution treatment) could reduce HCV transmission among PWID, but effective interventions to prevent HCV transmission among MSM have not been developed
- Scaled-up DAA treatment and effective harm reduction/preventive interventions are required to substantially reduce HCV prevalence among PWID and MSM, but high levels of reinfection due to on-going risk behaviour could compromise both individual- and population-level treatment benefits

Key points (2)

- The reported incidence of reinfection after SVR range from 2-6/100 PY in studies of PWID to 10-15/100 PY in studies of HIV-infected MSM
- Differences in reported reinfection estimates reflect heterogeneity in study populations with regards to risk behaviour, and variations in study design and applied virological methods
- Higher rates of reinfection might be expected in the DAA treatment era due to increased treatment access among people with on-going risk behaviour and less concerns for adverse effects of treatment
- Individual- and population-level strategies to address and prevent reinfection include acknowledgement without stigma, education and counselling, harm reduction optimization, scaled-up treatment in high-risk groups, treatment of injecting networks, post-SVR screening and rapid treatment of reinfections
- Future studies should assess the incidence of reinfection following DAA treatment and evaluate the feasibility of potential prevention and retreatment strategies

INTRODUCTION

In high-income countries, injecting risk behaviours among people who inject drugs (PWID) and high-risk sexual practices among men who have sex with men (MSM) are important routes of hepatitis C virus (HCV) transmission [1-3]. The majority of HCV patients in these populations have been chronically infected for many years and no longer take part in risk behaviour. Still, approximately one in four individuals with chronic HCV acquired through injecting drug use (IDU) have recently injected drugs [4] and thereby continue to be at risk of new HCV exposure.

People with on-going risk behaviour have been successfully treated for HCV infection [5-7]. However, treatment uptake was low during the interferon era, particularly among PWID [8, 9]. With the current availability of tolerable and highly effective interferon-free direct-acting antiviral (DAA) drugs, increased treatment rates and subsequent rising reinfection rates might be anticipated in high-risk groups.

The potential impact of reinfection is of considerable clinical and public health interest [10-12]. High levels of reinfection could compromise individual treatment benefits but also impede population efforts to limit the HCV epidemic. This review provides updated information on the epidemiology of HCV infection and the risk of reinfection after successful treatment in high-risk groups of PWID and MSM. Particular emphasis is given to the section on reinfection, in which methodological considerations, incidence rates, risk factors, and preventive strategies are discussed.

HCV EPIDEMIOLOGY IN HIGH-RISK GROUPS

HCV epidemiology among PWID

Prevalence of injecting

Globally, there are an estimated 14 million PWID (range 11.2-22.0 million) who are at risk of HCV infection as a result of injecting practices that may expose them to contaminated blood [13]. In most developed countries, IDU increased in the 1970s and 1980s and is now the main risk factor for HCV infection in these countries [14-16]. A recent review estimated the total number of current PWID across Europe to be 4.5 million [17].

Prevalence of HCV infection

Anti-HCV prevalence among PWID has been estimated at 67% worldwide, corresponding to 10 million anti-HCV positive PWID (range 6-15.2 million). While the prevalence varies greatly between countries, the majority report prevalence estimates above 60% [1]. This is the case in Europe, where the recorded midpoint prevalence estimates range from 21.1% to 90.5% with approximately half of all countries estimated to have 60% prevalence and above [1]. By region, the largest anti-HCV positive PWID populations are estimated to live in Eastern Europe (2.3 million) and East and South-East Asia (2.6 million); by country, the largest PWID populations are estimated to live in China (1.6 million), Russian Federation (1.3 million), and the USA (1.5 million) [1]. The total number of anti-HCV positive PWID in Europe is estimated to be 2.7 million, with 2.0 million being chronically infected [17]. A European systematic review estimates the viremic prevalence in PWID to be between 53% and 97% [18].

Incidence of HCV infection

In contrast to prevalence, no pooled global estimate of incidence among non-incarcerated PWID has been reported; however, a number of studies have reported incidence rates among selected local PWID populations. A systematic review (comprising data from nine European countries) identified 11 studies that reported a median incidence of 26/100 person-years (PY) among current PWID in the community [18]. A review and meta-analysis of HCV in prisons found a summary incidence rate of 16.4/100 PY among prisoners with a history of injecting [19].

Risk factors for HCV acquisition

Sharing needle/syringes is acknowledged to be the main route of HCV acquisition among PWID since direct percutaneous exposure to contaminated blood from a needle/syringe has been demonstrated to transmit HCV [20-22]. The risk of transmission associated with a given sharing event would, however, depend on a number of factors, such as the quantity of blood inoculated and the viral load. Ancillary injecting equipment (spoons/cookers, filters, and water) may also become contaminated with HCV during the process of preparing and injecting drugs. Sharing cookers and filters has been associated with an increased risk of HCV in epidemiological studies: while the probability of HCV transmission associated with the latter is likely less than that for sharing needles/syringes, the generally higher prevalence of sharing cookers/filters may increase their contribution to the proportion of new HCV infections [23-25]. While there is evidence of a decline in the rates of needle/syringe sharing in some countries, this risk behaviour nevertheless persists among PWID [26-28]. A similar decline has been seen in western European countries [29-32]; however, the prevalence of sharing needles/syringes may remain high in

Eastern Europe [33]. Furthermore, the sharing of ancillary injecting equipment appears to remain more prevalent than needle/syringe sharing [29, 34].

Harm reduction

Harm reduction is defined as the policies, programmes, and practices that aim to reduce the harms associated with the use of psychoactive drugs among people who are unable or unwilling to stop [35]. The main harm reduction interventions are generally considered to be sterile needle/syringe provision (NSP) and opioid substitution treatment (OST). There is evidence to support the effectiveness of NSP and OST in reducing injecting risk behaviour, and some evidence to support their effectiveness in preventing blood-borne virus transmission among PWID [36, 37].

More recently, studies have demonstrated that the combined impact of NSP and OST can produce a greater reduction in HCV transmission than either intervention alone [32, 38-40]. These interventions have been endorsed by national, regional, and international authorities for the prevention of HCV [41-44]. However, despite the availability of, and evidence for, effective harm reduction, most countries have not achieved a level of intervention coverage that would likely be required to curb new HCV infections: on a global level, there is generally poor coverage of interventions, with NSP coverage estimated at 22 sterile needles/syringes per PWID per year and OST coverage estimated at 8 OST recipients per 100 PWID. The highest NSP coverage is in Australia & New Zealand (202 needles/syringes per PWID per year) and the highest OST coverage is in Western Europe (61 OST recipients per 100 PWID) [45].

The experience of some countries that have achieved high levels of harm reduction intervention coverage is, however, that they can reduce, but not fully control, HCV transmission among PWID [32, 46]. This may be because high coverage needs to be sustained for decades in order to have an impact. For example, model projections have shown that, in a scenario of 40% viremic prevalence, reducing HCV prevalence by a third would require more than 60% coverage of both OST and high coverage NSP for 15 years [47]. More impact could probably be achieved through a treatment-as-prevention strategy: modelling studies have suggested that scaling up HCV therapy among active PWID (in addition to the existing harm reduction interventions) is necessary if substantial reductions in HCV prevalence over the next decade or two are to be made [48, 49].

HCV epidemiology among MSM

Prevalence of HCV infection

Cross-sectional studies have revealed an anti-HCV prevalence of 1-7% among MSM without a history of IDU compared to 25-50% among MSM with a history of IDU [50-55]. Further, HCV infection is more frequent among MSM with human immunodeficiency virus (HIV) infection (3-39%) than in those without HIV (0-19%) [51-53, 56-59]. The HCV prevalence among HIV-negative MSM without IDU is comparable to that of the general population [60-63].

Incidence of HCV infection

Beginning in 2004, an increase in the incidence of acute HCV infection was reported among HIV-infected MSM in Europe, North America, Australia, and Asia [60, 63-80] [11, 14-31]. A systematic review of these studies found that the incidence of acute HCV from 2000-2012 was approximately four times higher in HIV-positive MSM (0.61/100 PY) than HIV-negative MSM (0.15/100 PY) [81]. Data from 3014 HIV-infected MSM from 12 cohorts within the Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) collaboration showed that the HCV incidence increased from 0.55-0.81/100 PY in 1995 to 2.34-5.11/100 PY in 2007 [76]. Similar rises were observed among HIV-infected MSM in North America, Australia, and Asia [63, 75, 77, 79, 80]. One phylogenetic analysis revealed a large European-wide network of HCV transmission among HIV-infected MSM coinciding with the introduction of combination antiretroviral therapy and associated increases in sexual risk behaviours [82].

Risk factors for HCV acquisition

Permucosal (particularly sexual) transmission is the predominant route of HCV acquisition among MSM, especially in HIV-infected individuals [53, 83]. Use of mucosally administered recreational drugs (e.g. methamphetamines, ketamine, gammahydroxybutyrate, lysergic acid diethylamide) [62, 84-87] and high-risk traumatic sex practices, particularly unprotected anal intercourse, enema use prior to receptive anal intercourse, rectal trauma with bleeding, fisting, and group sex [58, 68, 72, 84, 85, 87, 88], have been identified as important behavioural risk factors for HCV transmission among MSM. The arrival of "chemsex" (i.e. injecting and non-injecting drug use to enhance sexual experience) might further promote HCV transmission among MSM [89]. Additionally, HIV and ulcerative sexually transmitted infections are important biological risk factors for permucosally acquired HCV [68, 84, 85, 87]. HIV infection increases HCV RNA levels [90] and promotes shedding of HCV in serum [91-93]. Ulcerative sexually transmitted infections disrupt the mucosal integrity of the genitourinary tract, facilitating HCV permucosal transmission [78, 84, 85, 87, 88, 94, 95].

Prevention

A recent study evaluating a dynamic HCV transmission model among HIV-infected MSM in the UK Collaborative HIV Cohort suggested that substantial reductions in HCV transmission could be achieved through scale-up of DAA drugs for the treatment of chronic HCV and effective behavioural interventions [96]. However, effective behavioural interventions to prevent HCV transmission have not been developed and tested in MSM. Targeted prevention messages that combine sexual health advice and avoidance of recreational drug use and which encourage MSM to discuss HCV with their partners might be helpful in preventing HCV infection [97-

99]. Repeated risk counselling on HCV transmission before, during, and after HCV treatment might also be beneficial for HCV prevention [7]. A recent randomized trial has shown that a reduction in high-risk sexual practices after a social network intervention led to a decline in the incidence of sexually transmitted diseases/HIV from 15% to 9% [100].

HCV REINFECTION IN HIGH-RISK GROUPS

General considerations

The lack of protective immunity

HCV reinfection after spontaneous clearance of the virus has been observed in chimpanzees [101, 102] and in humans [7, 103-114]. As reviewed elsewhere [115], some of these studies have demonstrated evidence of an augmented HCV-specific immune response following reinfection compared to after primary infection, suggesting that some immunological control may develop after repeated exposure to the virus. As this only seems to apply when exposed to a homologous HCV strain, one can at best hope for an acquired partial, but no protective, immunity against reinfection in clinical practice. The lack of protective immunity has also been evident in efforts to develop HCV vaccines, which so far have been complicated by the great genetic diversity of HCV, complex immunological responses to the virus, and the limited availability of animal models and at-risk cohorts [116, 117].

Heterogeneity and limitations of reinfection studies

Reinfection following sustained virological response (SVR) has over the last 10-15 years been documented in several studies in populations of PWID [118-127], prisoners [128, 129], and MSM [7, 98, 114, 130-132] (Tables 1 and 2). The reinfection incidence estimates reported in these studies have ranged considerably, reflecting differences in study populations with regards to risk behaviours, harm reduction coverage, and background viremic prevalence. Furthermore, most studies have been limited either by small sample sizes, short longitudinal follow-up, retrospective study designs, or insufficient risk factor assessment. Finally, differences in virological methods may also have biased the reported reinfection estimates and

accounted for some of the variation observed between studies. Collectively, all these aspects have made generalizability and comparisons between studies challenging.

Testing intervals - "the more often you look"

Some of the inter-study variability in reinfection estimates could be explained by differences in HCV testing intervals [133]. Observational data have demonstrated that reinfections often have a transient course with high rates of spontaneous clearance [112, 113, 134]. Thus, the event has probably generally been underestimated, as reinfection episodes with spontaneous clearance most likely will remain undetected unless HCV RNA is tested very frequently. Studies with wide testing intervals will therefore mainly capture those reinfections that have become persistent.

Sequencing methods - "the closer you look"

Recurrence of HCV RNA after SVR could result from one of three possible scenarios: late relapse of the pre-treatment majority variant, persistence/re-emergence of a pre-existing treatment-insensitive minority variant (either detected or undetected), or reinfection with a new viral strain not present at baseline [135, 136] (Fig. 1). This is an important distinction of both clinical and academic relevance, but correct classification is challenging and requires sensitive sequencing methods and robust phylogenetic analysis [137]. So far, there has been no standardisation of such methods, and studies employing insensitive techniques [7, 119-121, 124, 127-129, 138] may thus have had a potential to misclassify cases of late relapse as reinfection. On the other hand, among individuals with apparent relapse, it is very difficult to exclude the possibility of reinfection from the same source as the initial infection.

The relapse/reinfection distinction rests upon the detection of potential minority variants present in pre-treatment samples. This is relevant for individuals with on-going risk behaviour, who might harbour mixed infections resulting from either co-infections or superinfections due to repeated exposure to HCV [136]. Conventional line probe assays are widely used but have poor sensitivity for detection of minority variants that constitute <20% of the total virus population [139-143]. When using more sensitive methods [111, 144, 145], the reported prevalence of mixed infection in populations of PWID increases from <5% to 20-40%. In a study of MSM with HIV co-infection who had failed to respond to interferon-based HCV treatment, 15 of 15 participants had evidence of mixed infection when next generation sequencing (NGS) was performed [146]. Although the presence of mixed infection at baseline may compromise interferon-based HCV treatment outcomes [123, 147], its clinical significance remains controversial.

Most reinfection studies utilizing sequencing methods have applied majority population-based sequencing (i.e. Sanger sequencing) [98, 114, 122, 123, 125, 126], but NGS is emerging as the state-of-the-art method [146, 148]. Compared to population-based sequencing, NGS offers high throughput analysis with superior sensitivity, but at the same time generates large amounts of data that require costly bioinformatics and phylogenetic analysis. However, unless the whole genome is analysed, the choice of region to be sequenced and the exact design of PCR primers may influence the analysis and ultimately lead to misclassification bias [135, 136].

A pragmatic approach

In studies of low-risk populations, the reported risk of late relapse (i.e. post-SVR

recurrence of HCV RNA) is very low, with 5- and 10-year cumulative estimates of <1% [149]. In the presence of on-going risk behaviour, post-SVR recurrence of HCV RNA therefore most likely represents reinfection. In the absence of a virological gold standard to confirm a "true" reinfection diagnosis, we would therefore advise a pragmatic approach, taking post-treatment risk factors thoroughly into account.

Incidence of HCV reinfection after SVR among PWID

Reinfection after interferon-based treatment

Two pioneering studies among former and current PWID [118, 119] confirmed that HCV reinfection after SVR was indeed possible, albeit occurring at low rates. Most succeeding reports stated similarly low rates, and a meta-analysis [5] of the five first studies published from 2002-2012 [118-122] reported a pooled incidence of 2.4/100 PY. Among individuals with documented on-going risk behaviour after SVR, the pooled incidence was moderately higher (6.1/100 PY). However, the results from this meta-analysis should be interpreted with caution, as it was based on small studies of heterogeneous populations that included patients with relatively short follow-up time. Also, these early studies largely lacked sequencing methods to strengthen the reinfection diagnosis.

An Australian study among people with acute HCV infection [123], in which 76% had a history of IDU and 35% reported recent IDU at enrolment, pioneered sensitive sequencing methods using subtype-specific real-time PCRs for detecting mixed HCV infection. This study provided a detailed characterization of the natural history of reinfection and superinfection (i.e. the detection of a HCV strain distinct from the primary strain in those with virological persistence) among treated and untreated individuals. Among 67 individuals who achieved SVR, 12 cases of relapse and 5 cases of reinfection were detected. This generated a higher post-SVR reinfection rate (12.3/100 PY) than reported in previous studies, possibly reflecting the inclusion of participants with recently acquired HCV infection and still on-going high-risk behaviours. This study was also the first to identify independent risk factors for reinfection. Reinfection or superinfection occurred significantly more often in

participants with poorer baseline social functioning and in those who reported methamphetamine injecting compared to opiate injecting during follow-up. Interestingly, reinfection was not associated with baseline injecting status, indicating that prediction of reinfection may prove difficult in this population.

HCV infection is common in prison populations worldwide [19]. Although the prison setting may be considered as an opportunity for HCV treatment, it may also be an important site for HCV transmission and hence reinfections. The incidence of reinfection after HCV treatment provided in prison was investigated in an incarcerated cohort in Spain [129], of which 15% were HIV/HCV co-infected. Among 119 prisoners who obtained SVR, 9 (7.6%) were reinfected after a mean follow-up of 1.4 years, generating an overall incidence of 5.3/100 PY. Self-reported data on risk behaviour were unreliable, as four reinfected individuals reported no risk factors; thus, no reasonable reinfection estimate could be given among those who continued to inject drugs after treatment. However, reinfection was three times more common in HIV-positive than in HIV-negative subjects (13.4 vs. 4.0/100 PY).

Conversely, in another Spanish study of 84 HIV/HCV co-infected individuals [125], a much lower incidence of reinfection (1.2/100 PY) was found. This was an overall low-risk population mainly comprising former PWID or individuals on stable OST, but in the subgroup reporting risk behaviours during follow-up, 3 of 11 were reinfected (incidence 8.7/100PY).

A newly published comprehensive meta-analysis [150] included 14 articles or conference abstracts among PWID or prisoners and 4 studies of HIV/HCV co-

infected individuals from heterogeneous populations. Among a total of 771 PWID or prisoners, 42 cases of HCV RNA recurrence after SVR were observed. The pooled reinfection incidence was 1.9/100 PY, leading to an estimated 5-year risk of 10%. Among HIV/HCV co-infected individuals, the pooled incidence of reinfection was higher (3.2/100 PY), leading to an estimated 5-year risk of 15%. However, given that these estimates largely were based on data from small studies, there is still considerable uncertainty regarding generalizability and the actual long-term risk of reinfection.

In a recent Norwegian study [126], long-term reinfection rates were assessed in 94 individuals with a history of IDU who had achieved SVR in a treatment trial performed in 2002-2004. Notably, the study population was not a typical high-risk group, as six months of abstinence from IDU was required before treatment. Nevertheless, 39% had relapsed to IDU at some point after treatment. After a median of seven years after SVR, persistent reinfection was observed in 11% of individuals with a history of IDU prior to treatment (incidence 1.7/100 PY) and in 27% of individuals who reported IDU after treatment (incidence 4.9/100 PY). Although all episodes occurred among individuals with IDU after treatment, reinfection was not associated with any baseline variable; however, relapse to IDU was associated with younger age and low education level. While these estimates are in line with previous reports, direct comparison may be difficult due to the study's retrospective design with wide testing intervals and subsequent underestimation of all reinfection episodes. The study also highlights the vulnerability of viral sequencing of old serum samples with degradation of HCV RNA and low viral loads, which led to adequate sequences being obtained only in a minority of samples.

The long-term risk of reinfection has also been evaluated retrospectively in a large Scottish cohort of former and current PWID who had obtained SVR between 2000-2009 [127]. Risk behaviour post-SVR was assessed by registry linkage, and hospitalisation for an opiate- or injection-related cause during follow-up was considered a proxy for continued IDU. Among 277 individuals who were tested for HCV RNA after SVR, 7 reinfections were observed after a median of 4.5 years. Consistent with results from previous studies, the reinfection incidence was 1.7/100 PY among all included individuals and 5.7/100 PY among the proportion (11%) with continued IDU documented during follow-up.

Reinfection after DAA treatment

As HCV treatment for PWID becomes more feasible with interferon-free therapy, reinfection may become a more common event. The adverse events of interferon-based treatment have required close interaction with health care providers, offering opportunities for interventions aimed at achieving beneficial behavioural change [37, 151]. For some, interferon itself might even have provided a "cathartic" effect, resulting in efforts to protect one's SVR. One might therefore speculate that the potential for behavioural change will decrease in the emerging interferon-free era.

So far, no published studies have evaluated the risk of reinfection following DAA treatment, but some data has been presented as abstracts. Of 3004 patients who achieved SVR12 in the Phase 3 studies of sofosbuvir [152], which notably excluded patients with recent illicit drug use or OST, 12 cases of recurrence of HCV RNA were identified after 3 months of follow-up. Based on results from deep sequencing of the

NS5B segment, 7 of 12 cases represented reinfection while 5 of 12 cases represented late relapse. These findings suggest that among cases with HCV recurrence post-SVR12, most can be attributed to reinfection even in presumed low-risk populations.

Reinfection was also assessed in a recent study of elbasvir/grazoprevir in HCV patients receiving opioid agonist therapy [153]. Given that one-half of included individuals had detectable illicit drugs (excluding marijuana) in urine throughout the study, this population could be considered at high risk of reinfection. SVR12 was achieved in 184 of 201 (91%) patients and virological failure could be attributed to relapse in 7 patients and reinfection in 5 patients. The reinfection diagnosis was based on population-based sequencing of the NS3 and NS5A segments, supported by positive urinary drug screening in 4 of 5 individuals. Two of the cases with reinfection were subsequently HCV RNA negative, confirming that an important proportion of reinfections might clear spontaneously also after DAA treatment.

Incidence of HCV reinfection after SVR among MSM

Data on HCV reinfection among MSM are mainly limited to HIV-infected individuals. In addition, most studies have focused on reinfection following treatment of acute HCV infection [7, 98, 114, 130, 131], and few data are available on the incidence of reinfection after treatment of chronic HCV infection [7, 125]. However, in a British study [7] among HIV/HCV co-infected MSM that included both acute infections and cases of unknown duration, data on reinfection was reported for 46 individuals with unknown date of HCV infection. Among those, 12 (26%) were reinfected after spontaneous or treatment-induced clearance. The overall reinfection rate was 7.8/100 PY, slightly lower than among individuals with acute HCV infection.

High rates of reinfection in HIV-positive MSM following successful treatment of acute HCV infection have been reported in several studies [7, 98, 114, 130, 131]. In a study from Amsterdam [98], 11 of 51 individuals who achieved SVR were reinfected after a median follow-up of 1.3 years. The incidence of reinfection was 15.2/100 PY and the cumulative incidence was 33% within 2 years. The reinfection diagnosis was supported by sequencing of the E2-HVR1 region, and behavioural data, available in 21 MSM, showed that non-injecting drug use was more frequent in reinfected individuals. In a study from London [7], 27 reinfections occurred among 114 individuals with SVR after treatment of acute infection, yielding a reinfection rate of 9.6/100 PY and a 2-year cumulative rate of 25%. In addition, there were six second reinfections occurring after successful treatment of the 13 first reinfections. No behavioural data was reported in this study. The pooled reinfection rate for these two studies was 11.4/100 PY [131].

Two other studies estimated the frequency of reinfection after either spontaneous clearance or SVR during unreported periods of observation [114, 130]. In a Dutch study [130], 12 of 31 (39%) HIV-infected MSM who obtained SVR after treatment of acute HCV infection were reinfected. In addition, four MSM were reinfected during treatment, before reaching SVR. Another study assessed reinfection after SVR in four sites in Germany from 2001 to 2013 [114]. Among 302 MSM with either spontaneous or treatment-induced clearance of acute HCV infection, 48 first reinfections (16%) were detected. Of those, 42 achieved SVR, one was reinfected again before reaching SVR and five spontaneously cleared their reinfection. After a median time of 13 months after HCV clearance, there were 11 second reinfections (personal communication, P. Ingiliz). All episodes occurred in MSM who did not report injecting drug use.

In a recent European multi-centre collaboration [132], the rates of reinfection were estimated among 606 HIV-positive MSM with confirmed SVR or spontaneous clearance. Over 3 years of follow-up, 149 patients (25%) were reinfected, with an overall incidence rate of 7.6/100 PY. A second, third and fourth reinfection were detected in 69, 13 and 2 individuals respectively, and the incidence of second reinfection was 19.9/100 PY. The incidence varied between cities, with highest rates observed in Paris (21.8/100 PY). Behavioural data was not reported in this study.

Risk behaviours have not been systematically assessed in these studies, and factors associated with reinfection have therefore not been clarified among MSM. It is, however, conceivable that they are similar to those reported for primary HCV infection. In particular, the introduction of “chemsex” has likely facilitated HCV

transmission in certain sexual networks [89], driving a chain of primary infections and reinfections.

Comparison of reinfection rates among PWID and MSM

Based on existing data from small and heterogeneous studies of interferon-based treatment to former and current PWID, the incidence of HCV reinfection following SVR is approximately 2/100 PY in people with a history of IDU, increasing to around 6/100 PY in people with on-going IDU. The cumulative overall risk of reinfection calculated from all studies of PWID or prisoners reporting data on PY is 2.1/100 PY (43 reinfections over 2082 PY; Table 2). This is a significant risk, but still lower than rates of primary HCV infection reported in PWID outside the treatment setting [115].

Data on reinfection after SVR among MSM are also limited, but the reported incidence rates are considerably higher (10-15/100 PY) among HIV-infected MSM than among PWID, and may even exceed rates of primary HCV infection. The cumulative risk of reinfection calculated from studies of MSM reporting data on PY is 12.8/100 PY (38 reinfections over 296 PY; Table 2). These results, however, may not be generalizable to HIV-uninfected MSM. Moreover, epidemic outbreaks have been reported only in certain large cities, whereas acute HCV and reinfections continue to be uncommon among MSM in many areas with high prevalence of HIV/HCV co-infection [154].

There are some considerations to be made when interpreting the differences in reinfection rates between PWID and MSM. First, most studies among PWID were carried out in selected populations with chronic HCV infection, often including individuals without on-going risk behaviour at the time of treatment. Conversely, studies of MSM mainly included individuals with acute HCV infection who probably continued to be engaged in risk behaviours during and after treatment. Second, MSM

often have multiple risk factors for reinfection, including drug use as a sexual enhancer. Furthermore, HIV infection is a biological risk factor for HCV transmission more prevalent among MSM than among PWID. Table 3 summarizes important epidemiological differences between PWID and MSM.

Addressing reinfection

High cumulative rates of reinfection are to be expected as we enter the interferon-free treatment era. This could negate individual long-term treatment benefits and challenge the potential to prevent HCV-related liver disease morbidity and mortality in high-risk populations. High rates of reinfection would also allow continued HCV transmission and might compromise population-level treatment as prevention benefits [12].

Efforts to address and prevent reinfection should therefore be undertaken when providing HCV care for people with on-going risk behaviour. Acknowledgement of the problem without stigma and discrimination is the crucial first step; reinfections will occur and simply confirms that the target population is being treated. However, individual-level prevention of reinfection faces the same challenges as prevention of primary infection, and there are no data evaluating the impact of such interventions on reinfection. Nevertheless, all patients should be offered information, education and counselling about the risk of reinfection associated with high-risk sexual practices and unsafe drug use [37, 155]. Repeated safe sex counselling from health care providers and peers may be considered for HIV-infected MSM with high-risk behaviour [7, 97-100]. Combined harm reduction interventions should be optimized for all active injectors and HCV care should preferably be integrated in multidisciplinary settings [37, 156, 157]. The potential role of a prophylactic HCV vaccine for high-risk groups remains to be seen, but results from an on-going vaccine trial among PWID are highly anticipated [117, 158].

At the population-level, HCV treatment for high-risk groups could represent an opportunity for epidemic control [49, 159]. Individuals at high risk of reinfection are

probably also the ones most likely to transmit the virus forward. Targeted antiviral treatment for high-risk transmitters may therefore have great prevention potential, as these individuals, even if only temporarily, are kept out of the viremic pool. Despite the lack of empirical data, this perspective is supported by current international treatment guidelines that recommend prioritized treatment for PWID and MSM regardless of fibrosis stage [160-162].

As HCV incidence will depend on the viremic prevalence in a given population, rapid treatment scale-up in high-risk populations could be necessary to reduce the impact of reinfection over time [163]. Conversely, a slow scale-up could create an increasing number of susceptible individuals without reduction of the viremic reservoir. Consequently, early detection and retreatment of reinfections may be required to counteract the negative effects of reinfection at both individual and population levels. Individuals with a high probability of continued high-risk behaviour after SVR should therefore undergo annual HCV RNA screening within a multidisciplinary treatment setting and quickly get access to retreatment if reinfection is detected.

PWID rarely contribute to international HCV transmission, but instead engage in small local networks of injection partners [164, 165]. Injecting networks powerfully influence the transmission of HCV and could inform treatment-as-prevention strategies among PWID. In clinical practice, however, most often single persons within such networks are treated, resulting in a high reinfection risk. A feasible approach, both in settings of primary infection and reinfection, could therefore be to explore and treat whole networks using a “bring your friends”-strategy [166].

More data on reinfection are needed in a field rapidly moving forward. The incidence of reinfection following DAA treatment is unknown and should be assessed carefully in prospective clinical trials. Importantly, future research should evaluate the feasibility of potential prevention and retreatment strategies within controlled studies.

CONCLUSION

Current DAA treatment offers unique opportunities for reductions in HCV-related liver disease burden and epidemic control in high-risk populations of PWID and MSM. However, increasing rates of reinfection after successful treatment due to on-going risk behaviours should be anticipated and acknowledged without stigma. Constructive preventive strategies include education and counselling, harm reduction optimization, scaled-up treatment in high-risk groups including treatment of injecting networks, post-SVR screening, and rapid retreatment of reinfections.

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TABLES AND FIGURE LEGENDS

Table 1. Characteristics of studies of hepatitis C virus reinfection after sustained virological response among people who inject drugs and men who have sex with men

Study	Location	Design	SVR	Population	HCV infection	HIV	OST	Risk behaviour baseline	Risk behaviour post-SVR
Dalgard et al 2002 [118]	Norway	Retrospective follow-up	27	PWID	Chronic	0%	0%	0%	33%
Backmund et al 2004 [119]	Germany	Prospective cohort	18	PWID	Chronic	NR	39%	NR	50%
Currie et al 2008 [120]	United States	Prospective cohort	9	PWID	Chronic	56%	NR	0%	22%
Grebely et al 2010 [121]	Canada	Prospective cohort	35	PWID	Chronic	6%	43%	54%	46%
Grady et al 2012 [122]	Netherlands	Prospective cohort	42	PWID	Chronic	2%	93%	100%	26%
Grebely et al 2012 [123]	Australia	Prospective cohort	67	PWID	Acute	33%	NR	35%	38%
Hilsden et al 2013 [124]	Canada	Prospective/ RCT	23	PWID	Chronic	0%	27%	85%	NR
Pineda et al 2015 [125]	Spain	Retrospective cohort	84	PWID	Chronic	100%	24%	NR	15%
Midgard et al 2016 [126]	Norway	Retrospective follow-up	94	PWID	Chronic	0%	0%	0%	39%
Weir et al 2016 [127]	Scotland	Retrospective registry study	277	PWID	Chronic	NR	NR	NR	11%
Bate et al 2010 [128]	Australia	Retrospective review	53	Prisoners	Chronic	0%	NR	NR	NR
Marco et al 2013 [129]	Spain	Prospective-retrospective	119	Prisoners	Chronic	15%	100%	20%	NR
Lambers et al 2011 [98]	Netherlands	Retrospective/ Prospective	51	MSM	Acute	100%	NA	NR	NR
Martin et al 2013 [7]	United Kingdom	Retrospective	114	MSM	Acute /unknown	100%	NA	NR	NR
Vanhommerig et al 2014 [130]	Netherlands	Retrospective	31	MSM	Acute	100%	NA	NR	NR

PWID, people who inject drugs; MSM, men who have sex with men; SVR, sustained virological response; HCV, hepatitis C virus; HIV, human immunodeficiency virus; OST, opioid substitution treatment; NR, not reported; NA, not applicable

Table 2. Incidence estimates of hepatitis C reinfection after sustained virological response and applied methods in studies among people who inject drugs and men who have sex with men

Study	Population	SVR	FU, mean years	PYFU/PYFU post-SVR risk	Method	Testing interval, years	Reinfections	Incidence (overall/post-SVR risk), per 100 PY
Dalgard et al 2002 [118]	PWID	27	5.4	118/40	Genotyping Risk factors	1-7	1	0.8/2.5
Backmund et al 2004 [119]	PWID	18	2.8	51/24	Genotyping Risk factors	1	2	3.9/8.4
Currie et al 2008 [120]	PWID	9	3.6	38/3.5	HCV RNA Risk factors	0.5	1	0.56/1.89
Grebely et al 2010 [121]	PWID	35	2.0	63/38	Genotyping Risk factors	1	2	3.2/5.3
Grady et al 2012 [122]	PWID	42	2.5	132/32	Sequencing	0.5-1	1	0.8/3.4
Grebely et al 2012 [123]	PWID	67	1.1	140/56	Sequencing Risk factors	0-2	5	12.3/7.3
Hilsden et al 2013 [124]	PWID	23	1.8	36/NR	HCV RNA	NR	1	2.8/NR
Pineda et al 2015 [125]	PWID	84	2.8	330/NR	Sequencing Risk factors	0.5	4	1.2/8.7
Midgard et al 2016 [126]	PWID	94	7.1	593/206	Sequencing Risk factors	0.5-8	10*	1.7/4.9
Weir et al 2016 [127]	PWID	277	4.5	410/NR	Genotyping Risk factors	NR	7	1.7/5.7
Bate et al 2010 [128]	Prisoners	53	3.4	NR	Genotyping	NR	5	NR
Marco et al 2013 [129]	Prisoners	119	1.4	171/NR	Genotyping Risk factors	1	9	5.3/NR
Lambers et al 2011 [98]	MSM	55	1.3	72/NR	Sequencing Risk factors	0.25	11	15.2/NR
Martin et al 2013 [7]	MSM	114	1.6	224/NR	HCV RNA	NR	27	9.6/NR
Vanhommerig et al 2014 [130]	MSM	31	4.0	NR	Sequencing	0.5	8	NR

* Persistent reinfections

PWID, people who inject drugs; MSM, men who have sex with men; SVR, sustained virological response; FU, follow-up; PYFU, person-years of follow-up; PY, person-years; NR, not reported

Table 3. Differences in hepatitis C epidemiology among people who inject drugs and men who have sex with men

	PWID	**MSM**
HCV prevalence	High	Low*
Proportion of total HCV population	Large	Small
Access to HCV care	Poor	Good
Treatment of acute HCV infection	Rare	Common
Risk behaviours post-SVR	Variable	Prevalent
Transmission networks	Local	International
Reinfection rates	2-6/100 PY	10-15/100 PY

*Mainly limited to HIV-infected

PWID, people who inject drugs; MSM, men who have sex with men; SVR, sustained virological response; PY, person-years

Fig. 1. Recurrence of HCV RNA after sustained virological response could result from either (A) late relapse of a majority variant, (B) persistence/re-emergence of a pre-existing minority variant, or (C) reinfection with a new viral strain.

TW0, treatment week 0; EOT, end of treatment; SVR, sustained virological response; LOD, level of detection.