Epidemiology and diagnosis of acute hepatitis C virus infection
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GENERAL DISCUSSION
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In this thesis, the epidemiology of and tools for diagnosis of acute hepatitis C virus (HCV) infection were addressed among two groups at high risk for infection in high income countries: people who inject drugs (PWID) and HIV-infected men who have sex with men (MSM). We investigated incidence trends of acute HCV infection and reinfection among PWID and MSM, risk factors for sexual transmission of HCV among HIV-infected MSM, and different assays used for detection of HCV infection among HIV-infected MSM. Increased knowledge on these topics is likely to enhance prevention, testing, detection and management of acute HCV, in particular in the groups mentioned above.

Epidemiology of HCV infection among PWID

Since the discovery of HCV in 1989, the incidence of HCV among PWID decreased significantly in Amsterdam; during the late 1980s the incidence was >25 per 100 person-years (PY), during the 1990s a steep decline was observed to an incidence less than 5 per 100 PY, and since 2004 no incident HCV infections have been observed among ever injecting drug users in the Amsterdam Cohort Studies (ACS) [1,2]. One of the major contributors to this decrease in incidence is a high competing mortality rate due to HIV infection in HCV-infected PWID [3]. Other factors that are likely to have contributed to the observed decrease in HCV incidence among PWID are: the wide availability of comprehensive harm reduction programs including needle exchange and opiate substitution therapy; a steep decrease in the number of new injectors since the 1980s; ageing of the injecting population (often accompanied by a decrease in risk behavior); and the availability of HCV treatment. The latter is probably responsible for a minor part of the decrease, as treatment was introduced relatively recently and uptake was limited among PWID, because physicians had concerns about the patient’s adherence to therapy and their risk for psychiatric decompensation, premature mortality, and reinfection after successful treatment (because of ongoing risk behavior) [4–9]. However, we know from many studies that PWID can actually be successfully treated for HCV [10–13], thereby decreasing the time of infectiousness for several decades [14].

Our study, as described in chapter 2 of this thesis, showed that the incidence of reinfection was low (i.e., 0.76-3.42 per 100 PY) among PWID that were treated for chronic HCV infection in Amsterdam [15]. The results of our study were in line with other studies that evaluated HCV reinfection following SVR among PWID in Europe [9,16–18], the USA [19], Canada [20], and Australia [21]. Our study differed in several aspects: (1) follow-up time after clearance of a (primary) reinfection was included (as a person is at risk for reinfection as soon as the previous infection is cleared) whereas others (except [21]) calculated follow-up time from SVR, and (2) phylogenetic analysis was performed using pre- and post-treatment HCV sequences obtained from cases that were assumed to have a viral relapse following treatment. Although no reinfections were discovered among subjects that had a viral relapse (by definition) in our
studied, previous study among MSM showed that reinfections of the same genotype do occur in the first months after treatment completion, and can be distinguished using phylogenetic analysis (discussed later on in this chapter) [22]. Studies that assessed incidence of reinfection among PWID who cleared acute HCV infection, following either spontaneous clearance or treatment, reported reinfection rates of 1.8-46.8 per 100 PY [21,23,24]. Compared to the reinfection rate mentioned earlier in this paragraph this may seem relatively high, however the incidence of primary HCV infection among PWID is estimated to vary between 6.1-27.2 per 100 PY [23]. It may be possible that predominantly PWID with a low risk profile were treated in these studies. As the disease burden is expected to decline when both acute and chronic HCV infections are diagnosed and treated on a community-wide level, treatment should not be withheld PWID with HCV infection [14]. When scaling up treatment among PWID, prevention measures and education among PWID should be intensified in order to establish a substantial reduction of HCV infection risk. Intensified monitoring of PWID for HCV reinfection will be important.

Epidemiology of acute HCV infection among MSM

Although the HCV epidemic among MSM is relatively new, patterns differ between studies and regions. While one study claimed that the incidence of HCV has not changed over time [25], others agree that the incidence of HCV infection among HIV-infected MSM has increased notably after 2000 [26–32]. A recently published meta-analysis leaves no doubt that the incidence of HCV has increased globally (figure 1). In the ACS among MSM, the incidence of primary infection has reached a plateau phase with an incidence of around 12 per 1,000 PY [33]. In a study among 19 HCV treatment centers in the Netherlands, the HCV incidence in 2014 was estimated to be 11 per 1,000 PY [34]; these results were comparable to the incidence we found in the ACS in 2009-2011 and therefore strengthen the hypothesis of a stabilizing epidemic in the Netherlands. In addition, the overall (RNA and/or AB) prevalence of HCV among HIV-infected MSM attending a large STI clinic in Amsterdam seems to have peaked in 2008 at 20.9% and leveled off thereafter [35]. Unpublished updated data from these bi-annual surveys at the Amsterdam STI clinic conducted in 2011 and 2012 showed an overall HCV prevalence (HCV antibody and/or HCV RNA positive) in HIV-infected MSM of 9.4% and 8.9% respectively (T. Heijman, personal communication), again strengthening our hypothesis of a stabilizing epidemic among HIV-infected MSM. In addition, the ‘Hepatitis C in the UK 2015 report’ stated that between 2009-2013 the incidence of HCV infection among HIV-infected MSM in the UK had declined significantly to 2.3 per 1,000 PY [36]. However, this observation was solely based on case notifications. A recent study in an international cohort of HIV seroconverters also showed a stabilizing incidence in Western Europe. The incidence in Europe as a whole did not decline, mostly because of the ongoing increase in HCV incidence among MSM elsewhere in Europe [37].

While HCV infections with genotype 1 and 4 are most common among HIV-infected MSM,
our study in chapter 3 reported the emergence of HCV genotype 2b infections among HIV-infected MSM in Amsterdam. This genotype was not seen in this population before 2008, and the spread of genotype 2b among MSM in the Netherlands currently seems to be restricted to the Amsterdam area [34]. Our study also reaffirmed that the incidence of HCV infection among HIV-negative MSM is very low; no infections were detected during more than 10,000 PY of follow-up, leading to an incidence estimate of 0 with an upper 95% confidence bound of 0.3 per 1,000 PY in the period 1984-2012 [33].

Figure 1 Pooled HCV incidence rate among HIV-infected men who have sex with men between 1984 and 2015. Line: meta-regression with polynomial fit. The 95% confidence interval is shaded grey. Each dot represents an incidence estimate per calendar year, derived from the 17 studies included in the meta-analysis [38]. Copyright © 2015 Wolters Kluwer Health, Inc., reprinted with permission of the author (prof. H. Hagan) and the publisher.

Several hypotheses exist as to why the HCV epidemic is still largely restricted to HIV-infected MSM. One is that HIV-negative MSM are simply not screened. However, in one of the studies that argued this [39] the HCV prevalence among HIV-negative MSM was in fact comparable to the general population: 44 cases of acute HCV infection were detected among an estimated
34,657 HIV-negative MSM that visited this STI clinic in the UK, leading to a prevalence estimate of 0.13% (95% CI: 0.09-0.17). Similar observations of low prevalence among HIV-uninfected MSM have been made during bi-annual HIV surveys performed at the STI outpatient clinic in Amsterdam between 1995-2010 [35]. Because predominantly HIV-negative MSM with increased risk behavior (i.e., STI clinic attendees) were screened in this study, the prevalence of HCV infection is likely to be lower in the total HIV-negative MSM population. As cases of sexually acquired HCV infection have been reported in the absence of HIV in several studies [35, 39–43], it is of importance to continue to monitor the prevalence of HCV infection among HIV-uninfected MSM. Moreover, antiretroviral pre-exposure prophylaxis (PrEP) is the latest addition to HIV prevention packages, although it is not yet registered in the Netherlands. PrEP has proven to be very effective in randomized controlled trials performed among serodiscordant heterosexual couples, as well as among MSM who either continuously or intermittently used PrEP [44–48]. However, uptake of PrEP might impact the prevalence of HCV infection among HIV-negative MSM. Two PrEP studies [47,49] indeed reported incident HCV infections among MSM using PrEP. The incidence of HCV infection among PrEP users in a clinical practice setting in San Francisco was 6.6 per 1,000 PY; two out of 485 MSM were infected with HCV while on PrEP, and the only reported risk factor for infection was condomless anal sex [49]. In the PROUD study, an open-label randomized trial performed in the UK, six incident cases of HCV were reported among 512 participants [47]. Although risk compensation (i.e., an increase in risk behavior or a decrease in other prevention methods) has not been reported by trials so far [49], HIV-uninfected MSM on PrEP should preferably be monitored on a regular basis, for HCV as well as other STI [45].

In chapter 4 of this thesis, men that self-identified with MSM subcultures (leather, rubber/lycra, and jeans subcultures) were more often anti-HCV positive than MSM belonging to other subcultures [50]. This study is unique in that it included lifestyle characteristics of MSM that participated, and of their recent sex partner(s). In addition to the analysis of questionnaires, HCV sequences of viremic MSM were analyzed to investigate whether MSM of specific subcultures were infected with similar HCV strains. We found no evidence to support this hypothesis. A large part of the higher anti-HCV prevalence found among MSM that identified themselves with these subcultures is probably explained by increased sexual behavior within these subcultures. However, because HCV infection was not restricted to one or two subcultures, HCV preventive strategies are best directed to all HIV-infected MSM.

In chapter 5 of this thesis we studied risk factors for acute HCV infection among HIV-infected MSM and found that several sexual risk behaviors were associated with sexual transmission of HCV [51]. To our best knowledge, our study was the largest and most detailed case-control study identifying risk factors for sexual transmission in MSM. In addition, and unlike other case-control studies, we explored interactions of biological risk factors with specific sexual behaviors and sex-related risk factors (e.g., anal douching). We confirmed risk factors that
were identified in other studies, including unprotected anal sex, fisting, use of sex toys, injecting/snorting drugs, and concomitant or recent other STI (predominantly syphilis) [52–54]. In addition to these risk factors, we found an effect of lower CD4 cell count on acute HCV infection. Although the median CD4 cell count of both cases and controls was ≥500 cells mL⁻¹ and the absolute difference was not large, we found that the CD4 cell count was significantly lower well before co-infection with HCV. This finding excluded the possibility that the lower CD4 cell count we observed was in fact a result of HCV infection itself. A significant effect of lower CD4 cell count on acquisition of HCV infection has been reported by one other study, especially for those with a CD4 cell count <500 [25]. Other risk factors that have been reported by case-control studies, e.g., group sex, rectal bleeding and anal douching [52–55], were strongly associated in our univariable logistic regression analysis but lost significance in our multivariable analyses [51]. As especially MSM that report a combination of different sexual behaviors seem to be at increased risk for HCV infection [51,56], risk estimation for acute HCV infection may benefit from the use of an individual risk-score based on the measurement of sexual behavior acts. Ideally, the patient’s sexual behaviors are discussed during medical consultation, in order to decide on HCV testing. Pre-screening risk assessments in other forms have shown to improve screening efficacy [57]. However, because sexual risk behavior may not always asked by or disclosed to the treating physician, the use of a short self-administered questionnaire may assist in estimating the risk of HCV infection and advising testing.

Recently, an increase in the number of MSM that report having sex under the influence of drugs has been reported in the UK (since 2015 this is often referred to as chemsex) [58]. It is unclear whether there is an increase of crystal meth use among MSM in the Netherlands, as figures over time are lacking [58]. Recent reports from London, UK, raised concern because chemsex was described as a “perfect storm” for transmission of HIV and HCV [59–63]. This trend may spread to gay scenes in other cities like Berlin [64], as well as Amsterdam. Crystal methamphetamine (meth) is most frequently mentioned in relation to chemsex; in ‘The Chemsex Study’, a study performed in three London boroughs, 10.4% of MSM reported to have used crystal meth in the past 6 months [65]. In our study on sexual risk factors for HCV described in chapter 5, the proportion of MSM that had recently used crystal meth before or during sex was also significantly higher among MSM with acute HCV infection (19.5%) than among HIV mono-infected MSM (0.8%), however crystal meth before or during sex was not entered separately in the presented multivariable models; we chose to evaluate variables with either a potential direct or a facilitating effect on HCV acquisition [51]. A study among MSM in New York City between 2005-2010 also showed that having sex while high on crystal meth was a major risk factor for acquiring HCV infection [52]. GHB/GBL, mephedrone, ketamine and cocaine are also commonly associated with chemsex. Sex-related drug use has been associated with increased sexual risk behavior, and increased prevalence of chlamydia, gonorrhea, or syphilis among MSM and women [66]. Chemsex is likely to contribute to the spread of these STI including HIV and HCV, as the drugs can lead to a long-lasting high during
which unprotected sex with multiple partners can occur. In addition, an increased risk of potentially toxic drug-drug interaction between antiretroviral and recreational drugs has been described [64]. HCV transmission is also likely to be enhanced because some of the drugs used during sex parties (e.g., crystal meth, ketamine) can be injected (known as ‘slamming’) and needles may be shared. In a retrospective study performed by a sexual health clinic in the UK between 2006 and 2014, 20% of cases that acquired acute HCV infection through a sexual route reported to have injected drugs in the preceding months [67]. In our study on risk factors for HCV infection among HIV-infected MSM, injecting was reported by 12% of cases with acute HCV infection, but sharing needles was uncommon [51]. It is important to educate MSM about the risks of injecting drugs, even when needles are not shared. Sharing straws when snorting drugs was significantly associated with HCV acquisition in our study, while this might not necessarily be a direct transmission route. Further studies are therefore needed to clarify the relation we found between snorting drugs and HCV acquisition.

**Diagnosis of acute HCV infection**

As successful HCV antiviral therapies are becoming increasingly available, effective screening tools need to be implemented to find people that are unaware of their HCV infection. Because the detection of acute HCV infection is hampered by its asymptomatic nature, testing is ideally performed on a regular basis among those at highest risk for infection, even in the absence of reported symptoms. Apart from knowing who should be tested, guidelines on frequency of testing, and which tests should be used are of importance. The European AIDS Treatment Network (NEAT) [68] and Infectious Diseases Society of America (IDSA) [69] guidelines state that HIV-infected patients should be tested for anti-HCV at time of HIV diagnosis and monitored yearly thereafter. In addition, serum alanine transaminase (ALT) levels should be regularly assessed during visits to the HIV clinic (ideally 4-6 months apart) to evaluate the liver function. Dutch guidelines recommend yearly anti-HCV testing among HIV-infected MSM with risk behavior, and ALT levels should be evaluated at each visit for all. Follow-up HCV testing is then advised when ALT elevations are found. However, none of the proposed guidelines are currently fully implemented [70]. As a result, a substantial proportion of those infected with HCV might remain undiagnosed and untreated [71,72]. Moreover, as risk behavior is not defined it is important that in future revisions of the guidelines ‘risk behavior’ is specified more clearly. ALT values above the upper limit of normal (i.e., >40U/L) may indicate viral hepatitis when there is no alternate cause [73,74]. However, acute HCV infection does not necessarily lead to elevated ALT values, and ALT concentrations usually normalize within several weeks after acquiring HCV infection. Moreover, ALT elevations following HCV reinfection have been shown to be lower than during initial infection in recent studies among MSM [75,76], but also already in the early 1990s in chimpanzee studies [77]. The median time between infection and detectable anti-HCV levels is estimated to be 5-10 weeks and may be slightly prolonged among HIV-coinfected patients when compared to HIV-negative patients [78,79]. Therefore, when there is a clear suspicion of recent HCV infection, preferably an HCV RNA test should be
performed especially since major, or even subtle, elevations in ALT may be missed when this is monitored infrequently. In chapter 8 of this thesis we described a unique case with absence of detectable anti-HCV and normal ALT concentrations at clinic visits for more than 7 years [80]. This patient has now been successfully treated for his HCV infection and never had significant liver damage (M. van der Valk, personal communication).

Anti-HCV testing became available for HIV-infected MSM and MSM that opted out for HIV testing at the STI outpatient clinic of the Public Health Service of Amsterdam in November 2007, in response to the increased HCV prevalence found among HIV-infected MSM [81]. Because of financial constraints this service was stopped in May 2014. As a result, HIV-infected MSM were advised to visit their general practitioner (GP) or HIV treatment centre to get tested for HCV infection. However, a GP may be less approachable than an STI clinic that offers free and anonymous testing, and partner referral. Also, GPs may be less familiar with HCV infection because the prevalence in the general population in the Netherlands is low [82,83]. From the HIV clinician’s perspective, testing for HCV infection in patients without clinical signs or symptoms may not be indicated. Reinstatement of HCV testing for HIV-infected MSM at public health services is therefore advised.

As described in chapter 9, we have assessed sensitivity and specificity of the ARCHITECT HCV Ag assay (Abbott Laboratories, Abbott Park, IL, USA) for screening among HIV-infected MSM, as have other research groups [84–86]. The cost per test of this assay is significantly lower than of most assays that are developed for the detection of HCV RNA. Despite a lower sensitivity compared to commercial RNA assays [87], the clinical sensitivity of the HCV antigen test was 100% in all three studies. In other words, the yield was equal, while the window phase of detection was considerably shorter compared to testing for anti-HCV, due to the relatively long HCV seroconversion interval. The specificity of the HCV antigen test was >95% in two studies that also tested HCV-negative individuals [84,85]. Another promising and much needed addition to the current options for HCV testing is a point-of-care test. Several point-of-care tests have been developed that can detect anti-HCV, with sensitivity and specificity of up to 92.7% and 100%, respectively [88]. In addition, detection of anti-HCV, HCV core antigen, and HCV RNA, as well as determination of genotype was reported to be possible via collection of dried blood spots (DBS) [89]. Use of the DBS technique may improve uptake of testing and may simplify and expand the monitoring of hepatitis C. This has already been shown to be effective among PWID in non-clinical settings in the UK [90,91] and was considered cost-effective [92]. Among MSM, DBS and/or point-of-care could be used for testing at home, or even at gay venues (e.g., saunas, clubs). This way, thresholds for HCV testing can be lowered and case-finding may be increased. Future studies should investigate the potential of DBS/point-of-care tests for use among HIV-infected MSM. Cost-effectiveness should be investigated as well, as outreach projects can be costly.
While currently available antiretroviral therapies for treatment of HIV infection are well tolerated, a reduction in the number of contact visits among people with HIV infection would mean that patients are seen less than twice yearly. A decrease in the number of clinical visits by HIV-infected MSM also leads to a decrease in the sensitivity and specificity to detect HCV infection by using the relatively cheap ALT test. When used infrequently, the ALT test is not suitable as a monitoring tool, as has also been shown in chapter 9 of this thesis [85]. Frequent testing remains necessary to be able to diagnose patients early after (re-)infection with HCV. However, opinions on how often to test differ, while concise data or models to make an informed decision are lacking. Future research on this topic is therefore urgently needed to improve testing protocols for MSM.

HCV reinfection among MSM
Few studies so far reported on the incidence of HCV reinfection among HIV-infected MSM. Results from the MOSAIC study [32] and a research group from the UK [93] showed high reinfection rates following SVR of 15.2 and 9.6 per 100 PY respectively; more than 20 times higher than the incidence of primary HCV infection [38]. The rate of HCV reinfection was lower among men that spontaneously cleared a primary infection: 4.2 per 100 PY [93]. Anti-HCV testing is not suitable for detection of HCV reinfection, although we found a clear decrease in serum anti-HCV levels among MSM that were successfully treated for primary or reinfection with HCV. In some cases this resulted in seroreversion (i.e., a complete loss of anti-HCV), followed by an increase in anti-HCV after reinfection [79]. Reinfection occurred up to three times during follow-up, and sometimes shortly after completing HCV treatment of the previous infection. HCV-RNA testing is however more suitable for diagnosis of HCV reinfection. The frequency of testing for HCV reinfection is likely to influence the number of reinfections that are diagnosed, as model estimates among PWID suggested [94]. A recently published paper that reported results of DAA treatment among HIV/HCV-coinfected MSM with acute HCV infection in the Netherlands showed that as much as 25/99 (25.3%) men with acute HCV genotype 1 infection were treated for a reinfection [34]. The overall burden of HCV is likely to remain high if the incidence of primary HCV infection does not decline (as discussed in chapter 3 of this thesis), and the incidence of HCV reinfection is not reduced. Increased efforts to improve case finding and subsequent treatment of those with acute or chronic HCV infection are needed to bring the HCV epidemic to a standstill. In addition, behavioral interventions may contribute to a reduction of the risk of HCV reinfection.

Molecular epidemiology of HCV
Multiple studies in this thesis combined the fields of epidemiology and phylogeny. The combination of both disciplines has led to numerous new insights in studies investigating bacterial and viral infections. In this thesis two attempts were made to discover HCV transmission networks among HIV-infected MSM (chapters 4 and 6), but we found no convincing evidence that specific transmission networks with increased risk for HCV existed within the MSM
population; neither by using MSM subculture identity [50, chapter 4], nor by examining one’s HIV phylogenetic profile (chapter 6). In the latter study we investigated to what extent the topologies of HIV and HCV phylogenetic trees of HIV/HCV-coinfected MSM overlapped. This has been done in very few studies before, most likely as it requires the availability of a large number of sequences for analyses [95,96]. We performed this study combining data from HCV-infected MSM enrolled in the MOSAIC study with nationally collected data on HIV-infected individuals (the ATHENA cohort). A large number of persisting HIV transmission networks have been identified in the Netherlands [97]. The majority of the >100 separate transmission networks consisted mainly of MSM and some of these networks originated already early in the HIV epidemic and are still ongoing. Particularly the newer clusters were found to have higher HIV reproduction numbers [97]. However, MSM with evidence of HCV infection were not confined to specific, hypothetically “high-risk”, transmission networks. It might be that the time between HIV diagnosis and HCV infection was too long (the median duration was 3.3 years in our study) to observe overlap among the transmission networks of both epidemics. However, the time from HIV diagnosis to HCV infection decreased over calendar time in our study. As a shorter time between both infections increases the likelihood that one acquires both infections within the same transmission network, future studies may find overlap between the topologies of HIV and HCV phylogenies. If this decrease in duration between HIV and HCV infection persists, increased education about HCV infection and prevention measures should also target HIV-negative MSM, especially those at increased risk of contracting HIV.

The level of resolution in phylogenetic analysis is determined by the gene of choice, and is preferably based on the type or state of the epidemic. The highly variable E2 gene gives sufficient phylogenetic signal when diversification is limited, as is the case in the ‘young’ HCV epidemic among HIV-infected MSM [22,98]. In a more endemic state, such as among PWID in western Europe, less variable genes like Core or NS5B suffice to discriminate between relapse and reinfection, because the strains that circulate are more phylogenetically distinct [18]. A recent publication argued that sequence analysis of the Core-E2 region, a fragment covering 1,350bp, would be the most suitable for cluster analysis of HCV [99]. Finally, and although probably not needed for the majority of reinfections, next-generation sequencing of E2 sequences (or even full genome sequences) may be used to distinguish between relapse and reinfection by considering the possibility that a minority strain was already present during primary HCV infection and expanded during or after antiviral treatment [100–102]. This would especially be of interest when the period of viral suppression is short (or absent). However, study from our group demonstrated that multiple HCV strains rarely co-exist for longer periods of time, probably due to competition and/or superinfection exclusion [98]. Use of molecular epidemiological studies will remain important to see whether new HCV networks arise, and existing networks change. The recently initiated typing network Netherlands, known as Type-Ned, aims to improve monitoring of infectious diseases on a nation-wide level [103]. Currently, national surveillance databases exist for enterovirus, parechovirus and norovirus, and for the
methicillin-resistant *Staphylococcus aureus* (MRSA) bacterium. It would be recommendable to add hepatitis viruses, especially HCV, to this list.

**Treatment of HCV infection**

Peg-interferon and ribavirin are likely to become obsolete drugs in the treatment of HCV infection because other, shorter, and better tolerated therapies consisting of direct acting antivirals (DAAs) are increasingly becoming available. For the short term, all-oral DAA regimens have excellent efficacy and safety profiles, albeit these agents are still relatively expensive. Even HCV treatment of the historically ‘difficult-to-treat’ HIV-coinfected population seems to be as successful as in the HCV mono-infected population [104,105]. Treatment as prevention (TasP) has shown to potentially contain and slow the spread of HIV, apart from primary prevention measures [106]. In turn, HCV TasP may also be considered as an approach to reduce the number of new HCV infections among HIV-infected MSM, depending on the prevalence and uptake. Model projections by two research groups showed that a widespread implementation of HCV TasP, combined with integrated HCV testing, counselling and care has the potential to dramatically decrease HCV prevalence among PWID in Vancouver (Canada), Melbourne (Australia), Edinburgh (Scotland) [107], and in France [108]. However, the cost of DAA treatment is a major barrier in expanding treatment to the needed coverage. A recent study evaluated the possibility of HCV TasP as a strategy among MSM in the UK [109]. Model projections showed that if in the coming years 80% of MSM would be treated within a year of acquiring HCV infection, and 20% of those with chronic infection would be treated each year, HCV incidence may decline to less than 5 per 1,000 PY and prevalence would be reduced to less than 3% by 2025. In line with these findings, a recent modeling study from Switzerland suggested that if the levels of high risk sexual behavior among HIV-infected MSM do not increase further, treatment uptake and efficacy of DAAs will be able to significantly decrease the incidence of HCV infection over the next decade [110]. Observational studies are needed to measure the effect of TasP in the real world.

**HCV elimination**

Elimination of an infectious disease (i.e., reduction to zero of the incidence in a defined geographical area as a result of deliberate efforts) and eradication (i.e., a permanent reduction to zero of the worldwide incidence of infection) are the ultimate goals of infectious diseases control [111]. Eradication has been accomplished only once before: the last case of smallpox was seen in Somalia in 1977 [112] and therefore prevention efforts are no longer necessary. Another infectious disease that is now closer than ever to eradication is poliomyelitis (polio), for which a great worldwide effort has led to a 99% decrease; poliovirus type 2 has been declared eradicated in September 2015 after its last detection in 1999, and infections with type 3 have not been seen since 2012. Up to September 2015, Afghanistan and Pakistan were the only countries that reported active cases of polio in that year [113]. However, a major difference between smallpox, polio, and HCV is the availability of a vaccine. For HCV, no prophylactic
vaccine currently exists. Despite the availability of successful treatment, a vaccine is likely to be essential in eradication of HCV [114,115]. The search for an effective vaccine should therefore continue. Advances made in molecular vaccinology will enable to increase progress in the coming years [116]. Until then, prevention measures and treatment will form the larger part of the control of infection and disease. In resource-limited geographical areas, HCV treatment and especially the expensive DAA therapeutics, are not yet widely available. The western world should first focus on reaching a controllable state in which incidence, prevalence, morbidity and mortality are at a locally acceptable (low) level. Vigilance is important in maintaining this state. Eventually, elimination of HCV may be the next target to aim for.
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