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Modeling Combination HCV Prevention among HIV-infected Men Who Have Sex With Men and People Who Inject Drugs

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Abstract

People who inject drugs (PWID) and HIV-infected men who have sex with men (MSM) are key risk groups for HCV transmission. Mathematical modeling studies can help elucidate what level and combination of prevention intervention scale-up is required to control or eliminate epidemics among these key populations. We discuss the evidence surrounding HCV prevention interventions and provide an overview of the mathematical modeling literature projecting the impact of scaled-up HCV prevention among PWID and HIV-infected MSM. Harm reduction interventions, such as opiate substitution therapy and needle and syringe programs, are effective in reducing HCV incidence among PWID. Modeling and limited empirical data indicate that HCV treatment could additionally be used for prevention. No studies have evaluated the effectiveness of behavior change interventions to reduce HCV incidence among MSM, but existing interventions to reduce HIV risk could be effective. Mathematical modeling and empirical data indicate that scale-up of harm reduction could reduce HCV transmission, but in isolation is unlikely to eliminate HCV among PWID. By contrast, elimination is possibly achievable through combination scale-up of harm reduction and HCV treatment. Similarly, among HIV-infected MSM, eliminating the emerging epidemics will likely require HCV treatment scale-up in combination with additional interventions to reduce HCV-related risk behaviors. In summary, elimination of HCV will likely require combination prevention efforts among both PWID and HIV-infected MSM populations. Further empirical research is required to validate HCV treatment as prevention among these populations, and to identify effective behavioral interventions to reduce HCV incidence among MSM. **(AIDS Rev. 2017;19:97-104)**

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Key words

Antiviral treatment. Behavioral interventions. HCV eradication. HCV modeling. Hepatitis C prevention. HIV-HCV coinfection. MSM. PWID.

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Introduction

Globally, there are an estimated 115 million people with antibodies to hepatitis C virus (HCV), a disease resulting in substantial morbidity and mortality[1]. Of these, approximately 2.3 million (interquartile range, IQR: 1.3-4.4) are coinfected with both HCV and HIV[2]. If left untreated, HCV can result in liver disease, hepatocellular carcinoma, and death. The Global Burden of Disease estimated that hepatitis was the seventh most important cause of mortality in 2013, with roughly half of this morbidity and mortality attributable to HCV[3].

People who inject drugs (PWID) are a key risk group for HCV transmission, with an estimated 67% of PWID with antibodies to HCV globally, and many settings where the prevalence of HCV among PWID exceeds 80%[4]. Therefore, there is an urgent need for prevention interventions among this group. Additionally, in recent years there has been a rapid spread of HCV among HIV-positive men who have sex with men (MSM) documented in major urban centers in Europe, Australia, and the USA[5-7]. Although the burden of HCV is currently much lower than among PWID (HCV prevalence is generally at or below 10% among HIV-positive MSM[8]), increasing incidence[5,7] and prevalence[9] as observed in several settings indicates an emerging epidemic of particular concern. This expansion of HCV coincides with the expansion of other sexually transmitted infections among MSM, especially among HIV-positive MSM, and is thought to coincide with increases in risk taking among HIV-positive MSM on antiretroviral therapy.

Evidence for HCV prevention interventions

Harm reduction for PWID

As there is no vaccine for HCV, traditional harm reduction interventions have so far been the foundation of HCV prevention among PWID. Primary prevention interventions, such as opiate substitution therapy (OST) and needle and syringe programs (NSP), have been the backbone of the harm reduction response and are known to reduce the risk of HIV acquisition by 54% for OST (RR: 0.46; 95% CI: 0.32-0.67)[10] and by 34% for any exposure to NSP (RR: 0.66; 95% CI: 0.43-1.01)[11], with a stronger effect for NSP seen among high-quality studies.

Accumulating evidence indicates that OST and NSP can also reduce the risk of HCV acquisition, especially when used in combination[12]. A recent Cochrane Library systematic review and meta-analysis found that OST is associated with a 50% reduction in HCV incidence among PWID (RR: 0.5; 95% CI: 0.4-0.63)[12]. Despite conflicting studies on the impact of NSP (some finding exposure to NSP related to increased incidence, and others finding it associated with decreased incidence), the Cochrane review also found weak evidence that exposure to any NSP is associated with a reduction in HCV incidence (RR: 0.77; 95% CI: 0.38-1.54)[12]. The variability between studies may be partially explained by differences in exposure measure. In combination, OST and NSP can work synergistically to reduce HCV incidence; the review found exposure to OST and any NSP reduced HCV incidence by 71% (RR: 0.29; 95% CI: 0.13-0.65)[12].

HCV treatment as prevention

The HCV treatment landscape is rapidly changing, with the availability of highly effective, interferon-free, direct-acting antiviral (DAA) therapy, which can cure the disease in > 80% of cases for both HCV-monoinfected and HIV/HCV-coinfected individuals[13]. These all-oral, short duration (8-12 week), highly tolerable and effective DAAs have opened the door for the possibility of using HCV treatment as a means of prevention[14]. However, concerns persist about the potential for reinfection after successful treatment (sustained viral response, SVR). This is despite evidence indicating that SVR rates among PWID are similar to the general population[15], and that reinfection rates are relatively low[15], although these studies are small and participants involved are likely highly selected. Among HIV-infected MSM, high rates of reinfection after SVR (9-15 per 100 person-years) have been documented[16-18] and are therefore a particular concern.

Despite numerous mathematical modeling studies examining the potential impact of HCV treatment as prevention (discussed below), no empirical studies have evaluated whether scale-up of HCV treatment can reduce the incidence at a population level among PWID. Limited evidence exists among MSM; a recent analysis in the Netherlands showed a dramatic decline in HCV incidence among HIV-positive MSM from 1.12/100 person-years (95% CI: 0.91-1.37) in 2014 to 0.55/100 person-years (95% CI: 0.41-0.72) in 2016 after scale-up of DAA therapy[19]. However, it is unclear whether and how much this reduction was due to HCV treatment or other factors such as changes in risk behavior.

HCV behavioral interventions among MSM: possibilities and directions

Although harm reduction interventions may be relevant to some MSM who engage in injecting drug use (IDU), the observation of HCV among MSM with no history of IDU highlights the need for other prevention interventions. Case-control studies have identified numerous potential factors associated with HCV acquisition such as: fisting[20-24], rectal trauma with bleeding[24], condomless receptive anal intercourse[20,25,26], group sex[20,24,25], and IDU[21,25]. Additionally, several studies point to a combination of risks, such as drug use in conjunction with sex, being a particular risk factor for HCV. Indeed, a case-control study among MSM in New York found that "sex while high on methamphetamine" was independently and very highly associated with incident HCV infection (OR: 29)[26]. Additionally, two studies in Amsterdam found associations between HCV among MSM and consumption of gamma hydroxybutyrate (GHB)[21] or recreational use of cocaine, ecstasy, GHB, ketamine, amphetamine, or methamphetamine before or during sexual contact[23].

Despite the wide body of literature on behavioral interventions to reduce unprotected anal intercourse and HIV transmission among MSM[27], the data surrounding the effectiveness of interventions to prevent HCV transmission among MSM is lacking. A Cochrane review and meta-analysis in 2008 examined 40 behavioral interventions and found evidence that these interventions reduced occasions of or partners for unprotected anal sex by 27% (95% CI: 15-37) compared to no or minimal intervention[27]. In the USA, the Centers for Disease Control and Prevention (CDC) promotes 10 evidence-based behavioral HIV interventions designed for MSM[28]. One successful intervention geared toward substance-using MSM, Project ECHO, uses Personalized Cognitive Counseling to help participants identify and avoid risky sexual and drug-using behaviors[29]. In a randomized sample of HIV-negative MSM who reported sex after substance use in the past six months, the intervention reduced the number of condomless anal intercourse events with non-primary partners by 46% (RR: 0.56; 95% CI: 0.34-0.92) compared to the control group[29]. An intervention similar to Project ECHO could possibly be effective for HCV prevention due to associations found between sex/drug use and HCV infection.

The use of crystal methamphetamine among MSM, particularly with sex (a practice commonly referred to as "ChemSex") is associated with multiple partners during several episodes that can last for several days[30]. The MSM engaging in ChemSex are associated with more sexual partners, transactional sex, group sex, fisting, sharing sex toys, IDU, higher alcohol consumption, and the use of "bareback" sexual networking applications[31]. Those MSM engaging in ChemSex who inject may be less likely to identify themselves as PWID, less likely to disclose IDU, and less likely to present at traditional drug-use support services[32]. Hence, they are less likely to be exposed to harm reduction messages provided by the substance misuse healthcare sector.

In a number of international cities, ChemSex healthcare provision has intentionally shifted away from traditional substance misuse services towards sexual health/HIV clinics and MSM charitable organizations. This enables campaigns, NSP, harm reduction methods, and behavioral interventions that target MSM who engage in ChemSex to occur in settings already trusted and frequented by MSM[33,34]. For example, in one HIV/genitourinary medicine clinic in London, a pharmacist or doctor prescribing/dispensing HIV and/or HCV medicines to a newly diagnosed MSM patient will ask culturally appropriate questions to elicit disclosures about ChemSex and/or IDU[34]. The clinician will then either provide culturally appropriate harm reduction messages and tailored ChemSex packs that include safer injecting equipment and information[35], and discuss potential HCV transmission methods within a ChemSex environment with the patient and refer to on-site ChemSex behavior change support. This referral would be followed up after completion of HCV treatment to support the patient to avoid reinfection.

Behavior change support for MSM engaging in ChemSex differs from traditional models of drug addiction support. While drug-reduction plans, craving management, and relapse-prevention methods are universal, ChemSex motivations are often imbued with internalized homophobia and shame around homosexual sex, gay cultural/societal norms, sexual performance anxieties, religious, racial, and cultural attitudes to homosexuality, communication idiosyncrasies that exist on geo-sexual networking Apps, male body image/masculinity/femininity issues, and the shaming that can sometimes be normalized online. Successful behavioral interventions for MSM at risk of acquiring/transmitting HCV in ChemSex environments would need to address these issues with cultural sensitivity and competence.

Modeling HCV prevention among PWID

There is a growing body of literature using mathematical models of HCV transmission to explore the impact of prevention interventions, such as harm reduction, on HCV incidence and prevalence, particularly among PWID. Earlier studies considered the impact of decreasing syringe sharing[36-38] or the overall level of transmission risk[39-41] on the HCV epidemic amongst PWID, suggesting that levels of syringe sharing have to reach very low levels (< 1 per month) to achieve large reductions in HCV prevalence or incidence. A UK analysis from 2012 explicitly modeled OST and high-coverage NSP, and indicated that existing harm reduction (with approximately half of PWID exposed to harm reduction) has likely prevented very high levels of HCV among PWID (70% chronic HCV prevalence among PWID instead of the 40% observed today)[42], but that further substantial reductions would require potentially unachievable and/or unsustainable coverage of harm reduction (Fig. 1 A). A recent modeling analysis from Amsterdam[43] estimated that scale-up of harm reduction was required to reproduce the observed declines in HIV and HCV incidence, but a large proportion of the decrease may be due to other changes in risk across the same period. Additionally, another modeling study found that in settings with low or no levels of harm reduction, scaling up coverage of OST and high-coverage NSP can reduce chronic prevalence among PWID by up to 40% within 10 years in a range of settings (20, 40, or 60% chronic prevalence among PWID). However, further substantial reductions in prevalence (> 40% reduction) would require scale-up to very high levels of coverage for several decades (> 80% for 20 years), which is potentially unachievable or unsustainable[42].

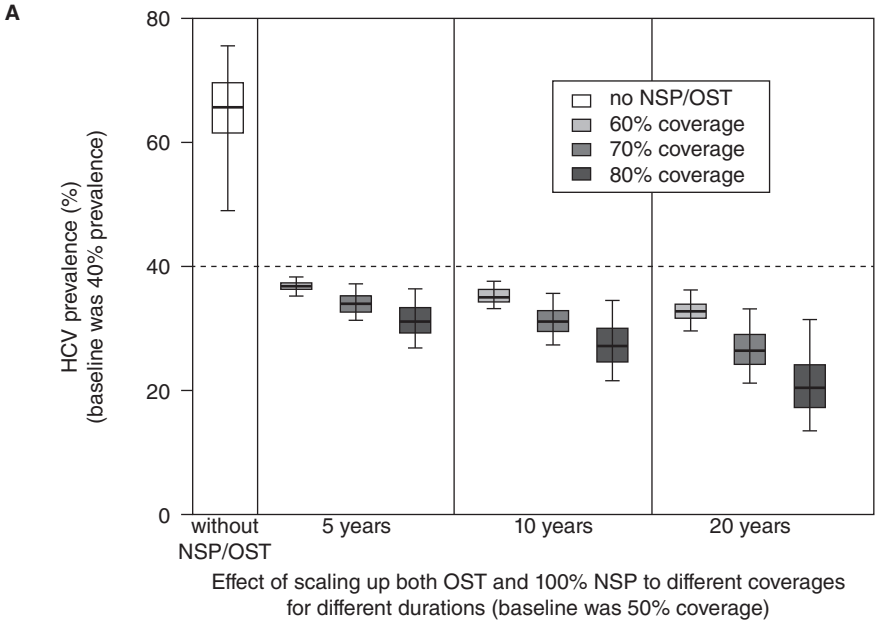
To date, there is no empirical evidence that scaled-up HCV treatment can reduce HCV incidence among PWID. However, numerous mathematical modeling studies have indicated that modest levels of HCV treatment for PWID can result in dramatic reductions in HCV incidence and chronic prevalence among PWID within 10-15 years in a range of prevalence settings in North America, Europe, Australia, and Vietnam[44-58]. Despite this encouraging evidence, in many settings the very low current treatment rates for PWID mean that treatment will likely have little impact[56,59,60] unless further scale-up is achieved.

Together, these studies point towards the need for a combined response for HCV prevention among PWID. This combination strategy would likely include harm reduction (OST and high-coverage NSP) in addition to HCV treatment. One modeling study showed that in settings with low or no harm reduction, combining harm reduction scale-up (OST and high-coverage NSP) alongside modest HCV treatment scale-up among PWID could reduce HCV incidence and chronic prevalence to elimination levels (> 90% reduction) within a decade in a range of prevalence settings[47]. A similar subsequent UK-based analysis confirmed that in a setting with already high levels of harm reduction, combination prevention with HCV treatment is required for elimination within a decade (Fig. 1 B)[61]. Two recent studies have explored the impact of combination prevention in particularly high-prevalence settings. A study in Athens found that treating 8% of PWID/year and expansion of harm reduction from 44 to 72% over 15 years could reduce HCV chronic prevalence by 90%[62]. Another study in Vancouver also found that HCV treatment (at a rate of 80/1000 diagnosed PWID annually) combined with harm reduction for those who achieve SVR could nearly halve HCV incidence within 15 years[56].

Modeling HCV prevention among MSM

In contrast to PWID, the absolute numbers of HCV/HIV-coinfected MSM are small and most diagnosed HIV-positive MSM are linked with care, so HCV treatment for prevention may be particularly feasible in this group. However, very high rates of primary and/or reinfection incidence[16-18] may limit the ability for HCV treatment alone to control the epidemic. Among HIV-positive MSM, combination prevention strategies incorporating behavioral interventions to reduce HCV risk with HCV treatment will help prevent reinfection, increase population impact, and may be necessary to reverse increasing trends in incidence.

The first modeling study of HCV among HIV-positive MSM examined the UK epidemic, projecting an increasing prevalence of HCV infection and estimating that existing levels of treatment are unlikely to reduce HCV chronic prevalence. However, the relatively stable incidence in the UK (as compared to the increases found in Switzerland) meant that scaled-up rates of DAA therapy could substantially reduce both HCV prevalence and incidence among HIV-positive MSM within a decade, but that combining behavioral risk reduction and treatment could enhance prevention impact compared to treatment alone[9]. Additionally, substantial and



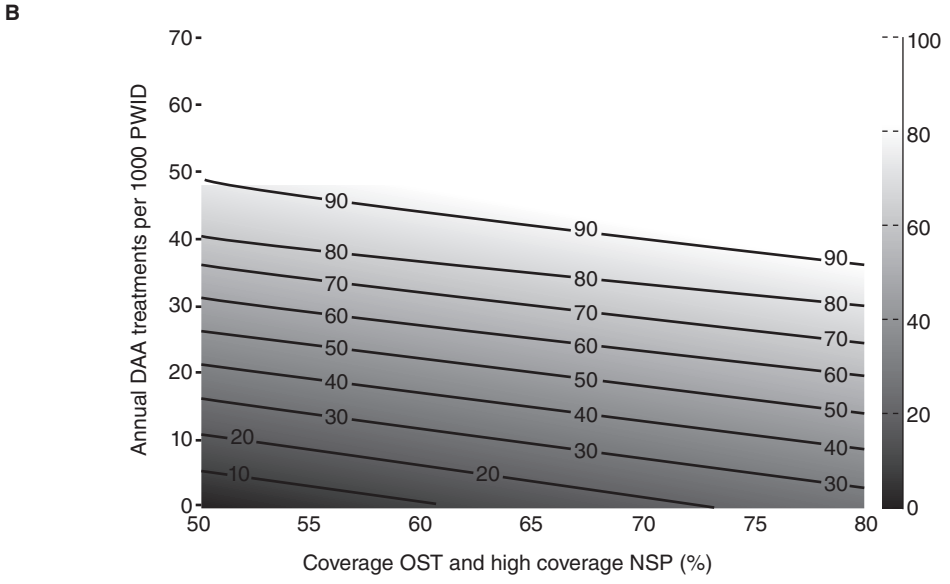


Figure 1. *Modeling projections of the combined effects of harm reduction alone (Figure 1 A) and combination harm reduction and HCV direct-acting antiviral therapy (Figure 1 B) on HCV prevalence among people who inject drugs in the UK[42,61]. (A) Impact of changing coverage of OST and high-coverage needle and syringe programs (100% NSP) from 50% of each to 0, 60, 70, and 80% over 5-20 years for a UK setting with a stable 36-44% baseline chronic HCV prevalence[42]. Middle line is median projection, limits of boxes are 25 and 75% percentiles, and whiskers are 2.5 and 97.5% percentiles of model projections. (B) Use of DAA therapy per 1000 PWID, OST, and NSP programs on HCV prevalence during 10 years in a population of PWID with 40% chronic HCV prevalence. Model projections assume a 90% sustained virologic response with future DAA therapy. Gradient lines show percentage reduction for specific combination of HCV antiviral treatment and OST and high coverage NSP. Heat colors show levels of HCV reductions from 0 (dark) to more than 80% (white)* (Figures reproduced with permission from The Lancet and Addiction). *NSP: needle and syringe programs; OST: opiate substitution treatment; PWID: people who inject drugs.*

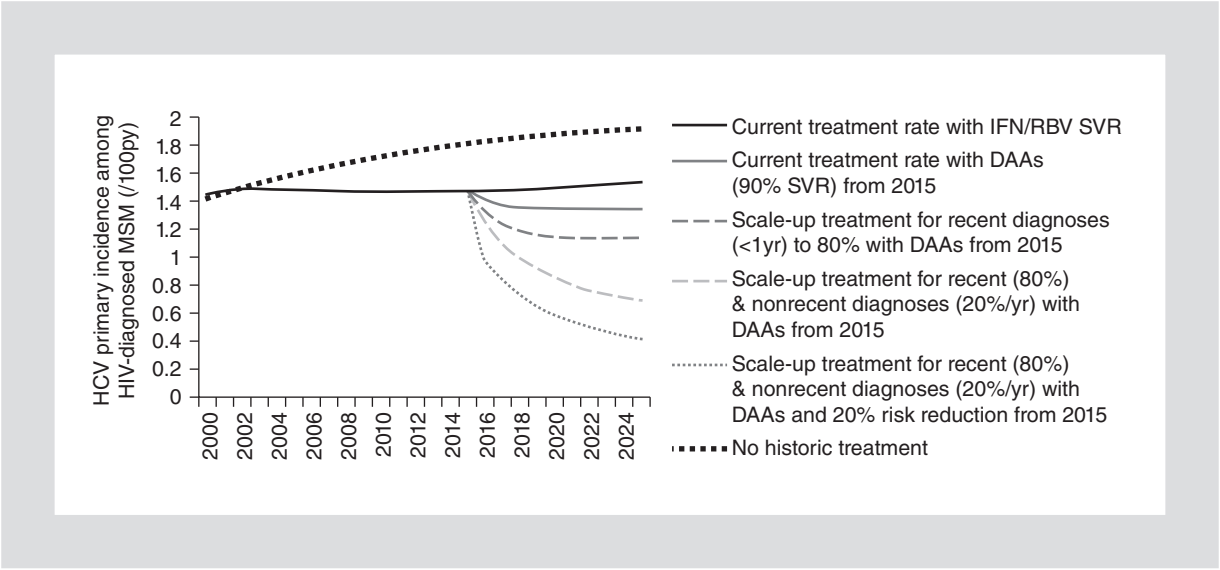


Figure 2. *Modeling projections of the combined effects HCV direct-acting antiviral therapy and behavior change interventions on HCV incidence among HIV-infected men who have sex with men in the UK*[9]. (Figures reproduced with permission from Clinical Infectious Diseases). *DAA: direct-acting antivirals; IFN: interferon; MSM: men who have sex with men; RBV: ribavirin; SVR: sustained virological response.*

immediate reductions in HCV incidence (> 30% within two years) require combination HCV treatment and behavior change (Fig. 2)[9].

A recent modeling study of the Swiss cohort[63] modeled continued increases in HCV incidence among HIV-positive MSM, as a result of steady increases in reported high-risk behavior over the past decade. If this trend continues, the model predicted that reductions in HCV incidence would not be achieved through HCV treatment alone, requiring also a stabilization of high-risk behavior (perhaps through behavioral interventions)[63].

Finally, preliminary modeling in the Netherlands indicated that DAAs could result in moderate reductions in HCV incidence among HIV-positive MSM (~ 30% within 15 years), but observation of a halving of incidence from 2014 to 2016[19] has raised excitement about the potential for treatment as prevention initiatives. Further modeling work will need to assess whether and to what extent the observed declines in incidence could be attributed to HCV treatment.

Discussion

Effective HCV prevention among key populations such as PWID and HIV-infected MSM will likely require a combination prevention approach in most settings. Among PWID, emerging evidence surrounding the efficacy of harm reduction, such as OST and high-coverage NSP, in preventing HCV acquisition strengthens the evidence that these strategies should be the backbone of any prevention response. However, modeling indicates that HCV elimination among PWID populations will only be achievable through the combination scale-up of harm reduction and HCV treatment. A combination prevention response will also be required for MSM; these strategies may require behavioral change support for MSM engaging in HCV-associated risk behaviors in addition to HCV treatment.

Unfortunately, a wide gulf exists between a comprehensive combination prevention response for PWID and the current global reality. Worldwide, harm reduction provision among PWID is low and the quality and coverage of these services is highly variable and often inadequate[64]. Additionally, although in theory modest scale-up of DAAs among PWID is possible, several barriers remain. The high cost of treatment remains a barrier, even in resource-rich settings. The prioritization of DAA therapy towards patients with more advanced liver disease, which is occurring in many settings[13,65], has meant that PWID, who tend to be younger with less advanced disease, are not prioritized. Mathematical modeling in the UK has shown that with the existing prioritization of advanced liver disease patients, little impact will be observed on the HCV epidemic among PWID[66]. Additionally, in the USA, many states have additional insurance reimbursement requirements based on drug and alcohol abstinence, countering existing guidelines, and further limiting the availability of HCV treatment for PWID[67].

Among MSM, there is a lack of robust evidence surrounding the efficacy of behavioral change interventions targeting HCV risk. It is possible that some interventions developed to prevent HIV transmission among MSM may also be effective against HCV, particularly those targeting substance-using MSM or prevention of blood-blood contact. There is an emerging body of literature examining the development of educational and counseling interventions targeted at MSM who engage in ChemSex, which may reduce the risk of acquiring HCV among this population. Further research is needed examining the development of culturally sensitive ChemSex behavioral change interventions, and the acceptability and efficacy of these in preventing HCV infection is required.

Finally, we note that there is very limited empirical evidence surrounding HCV treatment as prevention. Rigorous empirical studies showing that scaled-up HCV treatment for those at risk of transmission to reduce HCV incidence at a population level is required.

Conclusion

Mathematical modeling studies indicate that elimination of HCV will likely require combination prevention efforts among both PWID and HIV-infected MSM populations. Further empirical research is required to validate HCV treatment as prevention among these populations, and to identify effective behavioral interventions to reduce HCV incidence among MSM.

Declaration of interest

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