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Review

Eliminating HIV/HCV co-infection in gay and bisexual men: is it achievable through scaling up treatment?

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Abstract

Introduction: Broad availability of direct-acting antiviral therapy for hepatitis C virus (HCV) raises the possibility that HCV prevalence and incidence can be reduced through scaling-up treatment, leading to the elimination of HCV. High rates of linkage to HIV care among HIV-infected gay and bisexual men may facilitate high uptake of HCV treatment, possibly making HCV elimination more achievable in this group.

Areas covered: This review covers HCV elimination in HIV-infected gay and bisexual men, including epidemiology, spontaneous clearance and long term sequelae in the absence of direct-acting antiviral therapy; direct-acting antiviral therapy uptake and effectiveness in this group; HCV reinfection following successful treatment; and areas for further research.

Expert commentary: Early data from the direct-acting antiviral era suggest that treatment uptake is increasing among HIV infected GBM, and SVR rates are very promising. However, in order to sustain current treatment rates, additional interventions at the behavioral, physician, and structural levels may be required to increase HCV diagnosis, including prompt detection of HCV reinfection. Timely consideration of these issues is required to maximize the population-level impact of HCV direct-acting antiviral therapy. Potential HCV transmissions from HIV-uninfected GBM, across international borders, and from those who are not GBM also warrant consideration.

Keywords: gay and bisexual men, men who have sex with men, HIV, HCV, hepatitis C, coinfection, elimination.

1. *Introduction*

Over two million people are estimated to be HIV/hepatitis C (HCV) co-infected globally [1] and chronic viral hepatitis is a major cause of mortality among people living with HIV [2]. Key drivers of HCV transmission are injecting drug use, and high-risk sexual behavior among HIV-infected gay and bi-sexual men (GBM), often combined with injecting and non-injecting drug use to enhance the sexual experience [1, 3, 4].

HCV treatment has been transformed through direct-acting antiviral (DAA) medications that cure >90% of individuals using tablets over 8-12 weeks [5]. Modelling studies suggest that if HCV treatment can be adequately scaled, HCV prevalence and incidence can be reduced [6, 7]. In 2016 WHO set targets for the elimination of HCV as a public health threat by 2030 and whilst there is skepticism that this will be achieved globally, there is optimism that local elimination of HCV (micro-elimination) might be achieved in some settings, including HIV/HCV co-infected populations [8].

A key reason for optimism for HCV elimination in HIV co-infected population is this group are more likely to already be engaged in medical care compared with HCV-mono-infected population, due to increasingly high levels of HIV anti-retroviral therapy (ART) uptake [9]. This engagement in care provides an opportunity for broad coverage of HCV treatment, particularly given that DAA treatment is equally effective in co-infected and mono-infected populations [10, 11]. It also provides an opportunity for regular follow up of patients after treatment to detect reinfection events, with timely retreatment reducing the likelihood of ongoing transmission within the population.

2. *Defining HCV elimination*

Whereas disease eradication is defined as reduction of disease prevalence and incidence to zero globally such that no further control measures are necessary, disease elimination is

defined as reduction of disease prevalence and incidence to zero within a particular geographic area. Control of a disease involves reduction of disease prevalence, incidence, morbidity and mortality to a locally acceptable level [12, 13]. The WHO goals for the elimination of HCV elimination *as a public health threat* include a 90% reduction in HCV incidence and a 65% reduction in mortality by 2030. While termed elimination, these goals are essentially aimed at control rather than elimination of HCV. In this review the term HCV elimination is used to describe the WHO goals for the elimination of HCV as a public health threat.

3. Mathematical modelling of interventions for the elimination of HCV

Although there is currently very little empiric data on the effectiveness of interventions for the elimination of HCV, several mathematical modelling studies provide insight into the conditions required for HCV elimination. In the absence of a vaccine, effective and curative DAA treatment is a key requirement for HCV elimination. Broad access to DAA treatment irrespective of liver disease stage is a key feature of HCV elimination strategies. An individual-based model of disease progression and mortality before and after HCV treatment based on data from the Swiss Cohort study compared treatment at each of the five METAVIR fibrosis stages in HIV coinfected patients [14]. The percentage of individuals who died of liver-related complications was 2% if treatment was initiated in F0 or F1 and increased to 3%, 7% and 22% if treatment was delayed to F2, F3 or F4, respectively, highlighting the lifetime risk of liver-related mortality after successful DAA treatment in the context of cirrhosis.

In addition to the individual benefits of treatment prior to liver cirrhosis, there are also potential benefits at the epidemic level due to removing the risk of onward transmission with effective DAA treatment. Although theoretically these benefits could be partially ameliorated

by reinfection after successful treatment, epidemic modelling of DAA treatment scale-up in HIV diagnosed GBM in the UK suggested that if DAAs could be scaled up to 80% coverage within one year of diagnosis (including diagnosis in the acute and chronic disease stage), and 20% per year after that, the prevalence of chronic HCV could decline from approximately 10% to approximately 3% within 10 years *despite high rates of reinfection* [7].

Another epidemic model in Switzerland based on data from the Swiss cohort study [15] predicted that the effect of DAA treatment scale-up would depend on trends in high risk sexual behavior among GBM in care. From 2000-2013, increases in condomless anal intercourse with occasional partners and HCV incidence were observed in the Swiss cohort study. The model assumed that a proportion of GBM who reported unsafe sex would engage in HCV-related high-risk behavior (condomless traumatic anal intercourse, fisting, use of recreational drugs and group sex). The model predicted that if the observed increases in unsafe sex were to continue, then increasing treatment uptake would not be sufficient to curb increasing prevalence and incidence of HCV in HIV infected GBM and additional behavioral interventions would be required to prevent ongoing risk behavior after HCV treatment in addition to treatment scale-up [15].

A French model based on data from the French Dat'AIDS cohort included HIV infected GBM and other HIV infected populations. The model predicted that 30% treatment coverage would result in substantial reductions in HCV prevalence in all HIV infected groups other than GBM. In GBM, 50-70% treatment coverage would be required to curb observed increases in HCV incidence, with higher coverage leading to larger reductions in HCV incidence. Reductions in HCV prevalence could be achieved even if the size of the high risk group increased by 5-10% . Treating HCV in the acute stage (<6 months of infection) did not have a major impact on trends in prevalence [16]. Note that the increases in risk behavior in

the Swiss model (184% increase in the proportion in the high-risk group over 15 years) were much greater than the increases implemented in the French model [15].

An Australian agent-based model that incorporated data on types of sexual partnerships (regular, casual, and once-off partnerships) and allowed for heterogeneity in risk behavior, found that HCV elimination was achievable even in the context of a highly heterogeneous population. Multiple treatments were required for some individuals due to reinfection. The size of the high risk group was assumed to be static throughout the time period modelled [17].

The UK and Australian epidemic models were both among those diagnosed with HIV [7, 17]. However, the Swiss and French models included a proportion of the population with undiagnosed HIV, according to previous estimates of the undiagnosed/diagnosed split. Only those diagnosed (in the French model) or in HIV care (in the Swiss model) could be treated for HCV. Among those in HIV care, in the Swiss treatment scale-up scenario all received HCV treatment following diagnosis [15]. In the French study, treatment uptake scenarios ranging from 30-90% of those diagnosed were modelled [16]. The UK and Australian models considered time to HCV diagnosis among those diagnosed with HIV. In the UK model, those with HCV infection were diagnosed at the acute or chronic stage of HCV based on empirical data on HCV testing frequency among HIV diagnosed patients. In the treatment scale-up scenario, 80% of those diagnosed were treated within one year of diagnosis. Sensitivity analyses indicated minimal impact of importing HCV infections from undiagnosed HIV co-infected and HCV mono-infected populations [7]. Like the UK model, the Australian model assumed a variable HCV testing frequency based on empirical data. Among those diagnosed with HCV, the mean time to treatment was assumed to be approximately four years in the baseline scenario and six months in the treatment scale-up scenario [17].

4. *Pre-DAA HCV prevalence, incidence and risk-factors in HIV-infected gay and bisexual men*

A meta-analysis of 80 studies of HCV prevalence in HIV-infected GBM mainly conducted in North America (28 studies) and West Europe (28 studies) found that the midpoint prevalence of HCV antibody was 6.4% (IQR 3.2–10.0). Prevalence was highest in North America and lowest in East Asia and South and Southeast Asia. There was no data available in most of Africa, Eastern Europe and Central Asia, Central Europe, or the Middle East. The odds of HCV antibody in HIV-positive GBM versus HIV-negative GBM was 7.52 but there was considerable variation between studies (95%CI: 4.43–12.77, I^2=62·8%; p=0.030) [1]. Notably, the same meta-analysis found that Eastern Europe and Central Asia had the highest estimated burden of HIV-HCV coinfection in populations other than GBM, followed by Sub-Saharan Africa.

Among HIV-infected GBM, there is evidence that HCV incidence has increased over time since the late 1990s. Such increases have been observed in prospective cohort studies in Switzerland, the US and the Netherlands [18-20], although in the Netherlands incidence rates stabilized after 2005 [20]. Similar trends have been reported by a study of pooled data from European cohorts [21] and two meta-analyses [22-23], although these are limited by a lack of systematic HCV screening in many of the included studies. The increases in incidence observed from the early 1990s to 2010 are consistent with evidence from phylogenetic studies of Australian and European acute HCV infections detected in the early 2000s, which suggested that the majority of transmission occurred since 1996, coinciding with the introduction of ART [24, 25].

Although only low incidence of HCV has been identified in HIV uninfected GBM [13], the epidemic of HCV in HIV-infected GBM is thought to be driven substantially by sexual

transmission. In particular, several studies have identified high-risk sexual practices that involve increased risk of blood-to-blood or sperm-to-blood contact such as fisting, group sex, recent diagnosis with an STI, and sex-related rectal bleeding as risk factors for HCV transmission in HIV-infected GBM [23, 26-31]. However, HCV prevalence and incidence are significantly higher among those that report injecting drug use, and there is evidence of considerable overlap in risk practices in some studies [4, 23, 32, 33].

5. HCV spontaneous clearance in HIV-infected GBM

In the absence of antiviral therapy, HIV impacts on the natural history of HCV. In HCV mono-infected individuals, approximately 25% of primary HCV infections clear spontaneously [34] with variations by age [35], gender [36], host genetics (particularly, in the *IFNL4* gene, formerly *IFNL3* and *IL28B*) [36, 37], immune response [38-40], and HCV genotype [36]. A systematic review and meta-analysis of HCV RNA prevalence in individuals with HCV antibodies found that HCV RNA prevalence was higher among HIV co-infected participants (approximately 85%) compared to HCV mono-infected individuals (approximately 75%); however, this may be partially due to HCV reinfection [41]. Among those studies that have analyzed HCV spontaneous clearance in those with HIV infection and either documented HCV seroconversion or evidence of symptomatic HCV infection, spontaneous clearance rates have varied from 11-45% (Table 1). The majority of these are studies of clinically identified acute HCV infection among those receiving regular HIV care. They may be limited by censoring due to HCV treatment initiation prior to spontaneous clearance occurring on the one hand, and case ascertainment bias due to symptomatic patients being more likely to be diagnosed and also more likely to spontaneously clear on the other hand. Only one study found a spontaneous clearance rate that was greater than 25% in HIV infected participants; it was based on systematic analysis of stored sera from a prospective

cohort study of 101 GBM and found that 45% spontaneously cleared within two years [42]. It is possible that analysis of stored sera led to false positive results, leading to an overestimation of the number of acute HCV infections and therefore spontaneous clearance events [43]. The probability of spontaneous clearance of reinfection has also been found to be lower in the context of HIV infection (although in both mono-infected and HIV infected participants reinfections are more likely than primary infections to result in spontaneous clearance) [44]. On balance it is likely that spontaneous clearance is less common in HIV co-infected GBM than in HCV mono-infection.

This is consistent with evidence of impaired HCV-specific interferon γ (IFN-γ) production [45] in acute HCV in the context of HIV, and evidence that HCV seroconversion [46] and spontaneous clearance occur later in the context of HIV infection than in HCV mono-infection [47, 48]. Moreover, there are reports of occasional spontaneous clearance of chronic HCV after immune reconstitution following initiation of ART in those with favorable IL-4 genotypes (formerly IL-3 and IL-28) [49]. Symptomatic HCV (associated with spontaneous clearance) is also reportedly less common in those with HIV infection [50]. While the lower rate of spontaneous clearance observed in HIV coinfected GBM is likely partially attributable to the lower rate in males than females [34, 36], HIV-coinfection is also likely to play a role [45, 46].

Table 1: Studies of spontaneous clearance of acute HCV in HIV co-infected GBM

Study	**Study design**	**Acute HCV definition**	**Spontaneous clearance definition**	**n of N (%) cleared**
Thomson	Prospective cohort of	Documented	Undetectable RNA	17 of 112

2010 [51]	GBM presenting at an HIV clinic with acute HCV during an outbreak of HCV in GBM	seroconversion within 6 months	for 3 months	(15%)
Martin 2013 [52]	Retrospective analysis from two hospital HIV clinics (excluding females and those infected through injecting drug use)	Documented seroconversion within one year	Undetectable RNA for at least 24 weeks	31 of 145 (21%)
Grebely 2014 [36]	HIV infected participants in a collaboration of nine prospective cohorts at risk of HCV infection	Documented HCV seroconversion within two years or evidence of symptomatic HCV infection	Two consecutive undetectable HCV RNA test results >4 weeks apart	7 of 29 (24%)
Ingiliz 2014 [53]	Retrospective analysis from outpatient clinic (all GBM)	Documented HCV seroconversion within two years or evidence of symptomatic HCV infection	Not stated	22 of 207 (11%)
Ishikane 2014 [54]	Retrospective analysis from a single	High ALT followed by HCV seroconversion	Undetectable RNA within one year of	4 of 32 (13%)

	clinic (97% GBM)		acute HCV and remaining so thereafter	
Seaberg 2015 [42]	Multicentre prospective study of GBM, tested for anti-HCV retrospectively using systematically collected stored sera.	Documented seroconversion within study period	HCV RNA negative within 2 years after the estimated seroconversion date	45 of 101 (45%)
Newsum 2017 [43]	Prospective cohort study on HIV among GBM. Systematic screening of HCV.	Documented seroconversion within study period	HCV RNA negative within 2 years after the estimated seroconversion date	3 of 27 (11%)
Steininger 2017 [55]	Retrospective study of HIV-positive GBM diagnosed with acute HCV	Documented seroconversion within 12 months, documented rise in ALT and HCV RNA positive, HCV reinfection, HCV genotype switch, or other.	Two consecutive undetectable HCV RNA test results >24 weeks apart	23 of 213 cases among 178 participants (11%)

6. Liver disease progression in the context of HIV

In addition to being more likely to progress to chronic infection, liver disease progresses faster in those with HIV-coinfection compared to mono-infection. Among those with HIV, HCV is a major cause of death. In a large multicenter study of approximately 50 000 people living with HIV (44% GBM), liver disease was third most common cause of death after AIDS and non-AIDS related cancers other than hepatitis-related hepato-cellular carcinoma [2]. A meta-analysis of eight studies found that the relative risk of decompensated liver disease was approximately six times higher in the context of HIV coinfection (RR: 6.14, 95%CI, 2.86-13.20) and the relative risk of developing histological cirrhosis was approximately double in the context of HIV coinfection (RR: 2.07, 95%CI: 1.40-3.07) [56]. A second meta-analysis found that the effect of HIV infection on liver disease progression was partially but not completely mitigated by ART [57]. In both of these meta-analyses, the majority of study participants were PWID or acquired their infection through blood transfusion. In GBM, who are likely to acquire HIV prior to HCV and therefore may be immunocompromised during HCV infection, there is evidence that liver disease progression is faster than in those who acquire HIV after HCV. Rapid progression of liver disease has been observed in acute HCV infection among HIV infected GBM in several small prospective studies [33, 58-62].

7. DAA effectiveness in HIV-infected populations

However, although those with HIV coinfection are more likely to progress to chronic infection and more likely to progress to cirrhosis than HCV mono-infected individuals,

interferon-free DAA therapies are equally effective in HIV infected individuals as HCV mono-infected individuals [63-67]. In clinical trials, the SVR rates observed in HIV co-infected populations ranged from 86-96% (Table 2). These clinical trials had exclusion criteria relating to ART regimens and drug and alcohol use, potentially leading to limited generalizability in the broader HIV/HCV co-infected population [68]. Nonetheless, the SVR rates in real-world settings have been similar (87-99%, Table 2). However, in two Spanish cohorts, HIV infection was associated with lower probability of attaining SVR [69, 70]. In both cohorts, the difference in response rates to therapy was mainly due to relapse. A subsequent analysis of data from the German hepatitis C cohort found that those with CD4 count <350/IU and cirrhosis were less likely to attain SVR than other HIV infected participants [71]. However, a further analysis of the German hepatitis C registry which included almost 8000 participants, over 600 of whom were coinfected with HIV, found equivalent SVR rates in the HIV coinfected and HCV mono-infected groups despite a higher proportion of cirrhosis in the HIV coinfected group [72]. Equivalent treatment outcomes for HIV co-infected patients compared with HCV mono-infection combined with poorer outcomes in the absence of treatment theoretically allow for greater benefits of DAA treatment to be realized among HIV infected populations.

Acute HCV responds at least as well to therapy as chronic HCV, and this is reflected in current EASL and AASLD guidelines [73-76]. It is possible that shorter courses may be effective in acute HCV but research into ideal short-course regimens of all oral DAAs is ongoing [77-80]. Decisions to treat in the acute stage should balance the possibility of spontaneous clearance with the risk of onward transmission [75, 76]; however, it is sometimes difficult to differentiate between acute and chronic HCV. In the context of HIV, HCV diagnosis may occur after the first six months of infection due to infrequent HCV RNA monitoring and longer time to seroconversion in HIV infected patients [47].

Table 2: Sustained virological response rates following all-oral DAA therapy for chronic HCV in HIV infected patients

Study	Design	Participants	Number of participants	SVR (%)
Clinical trials				
Molina 2015 [81]	Multicenter single-arm open label study of sofosbovir and ribavirin (PHOTON-1)	Genotypes 1-4	274	86
Naggie 2015 [64]	Multicenter, single-arm, open-label study of ledipasvir and sofosbuvir (ION-4)	Genotype 1 or 4 with exclusions based on ART regimens	335	96
Rockstroh 2015 [82]	Multicenter, single-arm, open-label study of 12 weeks of grazoprevir and elbasvir (C-EDGE CO-INFECTION)	Genotypes 1, 4 and 6	218	96
Sulkowski 2016 [65]	Multicenter, randomised controlled trial of 24 weeks vs 12 weeks of ombitasvir, paritaprevir co-dosed with ritonavir,	Genotype 1 with exclusion based on ART regimens. Includes cirrhotic patients.	63	92

	dasabuvir, and ribavirin (TURQUOISE-1)			
Wyles 2017 [66]	Multicenter, single-arm, open-label study of 12 weeks of sofosbuvir and velpatisvir (ASTRAL-5)	Includes any HCV genotype and those with compensated cirrhosis.	106	95
Wyles 2015 [67]	Open-label study of 8 or 12 weeks of sofosbuvir and daclatasvir (ALLY-2)	Predominantly genotype 1 patients	203	92
Observational studies				
Beguelin 2017 [83]	DAA treatment in an observational cohort of people living with HIV	Swiss HIV cohort study	180	96
Bhattacharya 2017 [63]	Observational cohort analysis of the Veterans Affairs Clinical Case Registry	HIV/HCV genotype 1-coinfected veterans initiating 12 weeks of selected DAA regimens	996	91
Boerekamps 2017 [84]	DAA treatment in HIV/HCV co-infected patients in the Netherlands	ATHENA cohort which captures 98% of HIV diagnosed people in care in the Netherlands	702	85

Chkhartishvili 2017 [85]	DAA treatment in a linked clinical database of all HIV diagnosed patients in Georgia	Data from the national AIDS health information system in Georgia (AIDS HIS)	233	89
Del Bello 2016 [86]	Multicenter clinic-recruited prospective cohort study of those treated with SOF-containing regimens	Genotype 1 patients initiating treatment between December 2013 and December 2014	89	71
Hawkins 2016 [87]	DAA treatment in a large urban hospital-based clinic	Those enrolled in the viral hepatitis registry between January 2013 and June 2015.	54	89
Ingiliz 2016 [88]	Prospective cohort recruited from nine HCV treatment centers	Non cirrhotic genotype 1 patients	29	93
Mandorfer 2016 [89]	Retrospective analysis of patients treated with sofosvuvir/daclatasvir	Those with advanced liver disease	31	100
Milazzo 2016 [90]	Single-center clinic-recruited prospective cohort study	All those undergoing all oral DAA treatment from December 2014 to December 2015	58	91

Saeed 2017 [91]	DAA treatment in an observational cohort of people living with HIV	Canadian co-infection cohort study	202	87
Sogni 2016 [92]	Observational HIV/HCV coinfection cohort study	Cirrhotic patients in the HEPVIH cohort	189	93

*74% of 1284 participants who ever received HCV treatment were MSM but the percent of participants receiving DAA treatment who were MSM was not reported.

8. Access to DAA therapies

High rates of HIV/HCV coinfection in GBM have been observed in North America, West Europe and Australia [1]. Although several West European countries and Australia already have universal access to DAAs [93], a recent review of 34 European countries revealed barriers to accessing DAA therapy due to restricted reimbursement according to liver disease stage [94]. Limiting prescribing to specialists only was also identified as a major impediment to access. In the US, while guidelines no longer recommend treatment prioritization, insurance companies and individual state health systems continue to restrict therapy for those with less advanced disease. A recent study [95] revealed heterogeneity in reimbursement criteria for sofosbuvir across state fee-for-service Medicaid plans, including restrictions based on prescriber type, liver disease staging, HIV co-infection, and drug or alcohol use with 50% requiring a period of abstinence and 64% requiring urine drug screening.

In countries with universal and subsidized access to DAAs, there have been reports of high levels of treatment uptake within HIV infected populations [83, 85, 96-100]. In the Canadian Co-infection cohort, treatment uptake increased from 8 per 100 person years to 28 per 100 person years. GBM were approximately twice as likely to initiate treatment compared to heterosexual men [91]. Among those in the Dutch ATHENA cohort diagnosed with HCV prior to February 2017 (including those treated with interferon-based therapies, DAA therapies and those remaining untreated), GBM were less likely than other patients to remain untreated [84]. In the Netherlands, broad access to DAAs was introduced in 2014 and was accompanied by considerable increases in treatment uptake. The incidence of HCV in a large cohort of HIV infected patients (including GBM and other groups) was approximately 50% lower in 2016 compared to 2014 despite increases in syphilis incidence in the same period [96]. More research is required to determine whether this decrease is indicative of a long-

term decreasing trend. In contrast to the data from the Netherlands, the incidence of HCV in GBM in a large multicenter clinical cohort of HIV-infected individuals (the Dat'AIDS cohort) in France increased from 0.5 per 100 person-years in 2012 to 0.92 per 100 person-years in 2016 despite substantial increases in treatment uptake. By the end of 2016, 82% of those with HCV antibodies in the Dat'AIDS cohort had either spontaneously cleared or attained SVR through treatment. However, although there were substantial increases in treatment uptake from 2014 when DAAs became available in France to those with advanced liver disease, these data are from prior to universal access to DAA therapy [100]. More research is required to determine whether these trends will continue as DAA treatment scale-up continues in France and to monitor potential changes in HCV incidence in other jurisdictions.

9. Reinfection following HCV treatment in HIV co-infected GBM

One potential challenge to HCV elimination in HIV co-infected GBM is the high rate of reinfection that has been observed in this group following HCV antiviral therapy. Studies from the pre-DAA era have reported reinfection rates post treatment ranging from 1.6 to 15.2 per 100 person-years (Table 3) [44]. There are fewer data available from the DAA era. A conference report on a German multicenter clinical cohort of approximately 1500 participants including 166 GBM, found that 11% of GBM and 1% of people who inject drugs became reinfected during follow-up. The median time to reinfection was 41 weeks (IQR: 25-67) [101]. A French multicenter clinical cohort found that the reinfection rate in GBM after spontaneous clearance or HCV treatment was stable from 2012-2016 (2.52–2.90 per 100 person-years) [100]. Among those that report rates of reinfections following spontaneous clearance or treatment of reinfection, the subsequent reinfection rates have been even higher (ranging from 18.8-23.2 per 100 person-years, Table 3). The rates of reinfection in HIV-

infected GBM were higher than reinfection in PWID and other high-risk groups following treatment which had rates of approximately 2.2 per 100 person-years according to meta-analysis [102]. One explanation for the high rates of HCV reinfection and repeated reinfection in HIV-infected GBM is that HCV transmission may be concentrated within a small group of GBM who engage in high risk sexual and drug-related behaviors. That is, those at risk of reinfection have already been infected at least once with HCV so are more likely to engage in high risk sexual and drug-related behaviors than those who have never previously been infected, leading to higher reinfection rates than primary infection rates. The vast majority of these data are from the pre-DAA era, and more research is required to determine the rates of reinfection after treatment with DAAs. These may be substantially different from the rates of reinfection in the interferon era given that treatment uptake has increased considerably.

Table 3: HCV reinfection following spontaneous clearance or antiviral therapy in HIV infected GBM

Study	Participants	Reinfection definition	Clearance definition	N	Cases	Reinfection rate per 100 PY (95% CI)	Second reinfection rate per 100 PY (95% CI)
Lambers 2011 [107]	HIV-infected MSM recruited from HIV outpatient clinics. Interferon-era data.	Sequencing	ETR	56	11	15.2 (8.0-26.5)	
Martin 2013 [52]	MSM recruited from HIV clinics, excluded if primary mode of transmission was IDU or contaminated blood products. Interferon-era data.	Detectable viremia, or genotype switch prior to SVR	SVR	114	27	12.0 (84.06–169.47)	
Martin	MSM recruited from HIV clinics, excluded if primary mode of	Detectable viremia	Spontaneous	31	5	4.2 (1.7–10.0)	

2013 [52]	transmission was IDU or contaminated blood products. Interferon-era data.		clearance				
Thomas 2015 [108]	HIV-infected MSM attending hospital HIV treatment clinic. Interferon-era data.	Sequencing	Acute infection – includes superinfections	51	19	5.4 (3.3-8.3)	
Ingiliz 2017 [44]	Hospital-recruited HIV infected MSM. Interferon-era data.	Detectable viremia	Spontaneous clearance or SVR	552	143	7.3 (6.2-8.6)	18.8 (12.9–27.5)
Martinello 2017 [109]	Hospital-based clinical trials of HCV treatment in acute HCV. Predominantly interferon-era data.	Sequencing	ETR	64	6	8.9 (4.0-19.7)	
Young 2017 [110]	Recruited from HIV clinics and community. Most GBM were former IDU.Predominantly interferon-era	Detectable viremia	SVR	85	6	High-risk GBM: 2.6 (6-66), Low risk GBM: 1.6 (4-	

	data.					38)
Ingiliz 2017b [101]	Multicenter clinic-based prospective cohort, DAA era data.	Detectable viremia after SVR12 or genotype switch before that	SVR	166	19	Not reported
Pradat 2018 [100]	Multicenter clinic-based prospective cohort, data pre-DAA era (2012-2013) and after DAA approval but prior to universal access to DAAs	Detectable viremia after SVR12 or spontaneous clearance or genotype switch before that.	SVR or spontaneous clearance	3406	68[a]	2012: 2.52 2016: 2.90 (95% CI not reported)

a.73 reinfections in 68 individuals

10. Other interventions to prevent HCV primary infection and reinfection in HIV infected GBM

Epidemic models of HCV elimination in HIV infected GBM suggest that behavioral interventions to prevent HCV transmission may be required in addition to DAA scale-up in some contexts, particularly if the group practicing HCV risk behaviors is expanding [15]. Even in contexts where it may be possible to reach HCV elimination targets without behavioral interventions, modelling suggests that effective behavioral interventions could reduce the time taken to achieve HCV elimination [7]. However, although there are several evidence-based interventions for reducing condomless anal intercourse among HIV infected participants [103-105], the efficacy of these interventions for reducing HCV-related risk behaviors is not clear. Similarly, the effectiveness of harm minimization interventions for reducing drug related risk behaviors is unclear in GBM [106]. More research is required to identify effective interventions for HCV prevention in GBM.

11. Directions for future research

In order to assess whether it will be possible to eliminate HIV/HCV co-infection in GBM through scaling up treatment, there are several knowledge gaps that require additional research. Continued monitoring of HCV-related risk behaviors, primary incidence and reinfection incidence in GBM is crucial in order (a) to determine whether HCV-related risk behaviors and HCV incidence prior to introduction of DAA therapies have continued to increase after 2010, (b) to estimate reinfection incidence rates after DAA therapy and trends in incidence rates over time, and (c) to identify sub-groups at elevated risk of reinfection for risk reduction interventions and additional post-treatment monitoring. Critically, HCV elimination requires treatment uptake to reach or exceed specific targets for treatment-as-prevention to be effective. Additional interventions to increase HCV diagnosis rates and

linkage to care may be required in order to maintain treatment uptake [111] with ongoing monitoring to assess if prevention, testing and treatment levels are sufficient to achieve elimination. Further research to identify barriers and enablers of diagnosis and linkage to care in the DAA era will be required in order to develop effective interventions. These interventions, as well as preventive interventions to reduce risk of HCV infection and reinfection, and to identify and re-treat reinfections, should be evaluated using randomized controlled trials or longitudinal cohorts where possible.

Although HCV prevalence and incidence have generally been thought to be low in HIV-uninfected GBM, recent research from the Netherlands demonstrates that 5% of GBM receiving pre-exposure prophylaxis to prevent HIV were infected with HCV at baseline. The HIV-infected and uninfected GBM were infected with similar HCV strains, strongly suggesting that there was ongoing HCV transmission between HIV-infected and HIV-uninfected GBM [112]. A subsequent mathematical modelling study parameterized with UK data found that behavioral factors (preferential mixing by HIV status and heterogeneity in sexual risk behavior) explained the high HCV prevalence observed in HIV-infected GBM better than biological factors (increased HCV transmissibility and lower rates of spontaneous clearance in those with HIV infection) [113]. More research is required to determine whether there may be a high-risk subset of HIV-uninfected GBM who are at risk of HCV outside of the Netherlands. If this is the case, it may be necessary to resource HCV screening, diagnosis and treatment among high-risk HIV-uninfected populations at the same time as HIV-infected populations in order to maintain reductions in HCV prevalence among HIV infected populations in the long-term.

A further consideration is whether HCV can be eliminated from GBM without addressing HCV infection in other populations. A phylogenetic analysis of genotype 4 acute HCV

infections in Germany using Dutch, English and French reference sequences, found that HCV infections from all but one German GBM belonged to large GBM-specific HCV clusters containing GBM from all four European countries. There was no overlap between clusters containing GBM and other risk groups [114]. Australian studies have identified transmission clusters including HIV infected and uninfected participants and different modes of acquisition (sexual and injecting drug use), but male-to-male sex was only reported for HIV-infected participants so it is not possible to determine whether there was evidence of transmission between GBM and other participants [25, 115]. Ongoing monitoring of phylogenetic clustering is required in order to determine whether GBM are at risk of acquiring HCV infection from other populations. Previous phylogenetic evidence indicated possible transmission between countries among GBM in England, the Netherlands, Germany and France, suggesting that cooperation between countries may be required to achieve local HCV elimination [24].

Finally, even if HCV can be eliminated from GBM in high-income countries, it is possible that HCV incidence in GBM will persist in other parts of the world. Currently HCV/HIV prevalence in GBM is unknown in much of the world, including in central Asia, Eastern Europe and Sub-Saharan Africa, where HCV/HIV coinfection burden is high in populations other than GBM [1]. While the majority of HIV transmissions in these regions are attributed to injecting drug use and heterosexual sex, the burden in GBM is likely to be high in at least some countries, and may have been masked by the larger epidemics in heterosexual populations and PWID [116-118]. Understanding the HCV/HIV coinfection burden among GBM is a crucial first step to elimination in these regions. Stigma and discrimination against GBM is a major barrier to improving HIV care in many low- and middle-income countries and is also likely to be a significant barrier to HCV elimination [119].

12. Conclusions

In several countries in Western Europe, North America and Australia the prevalence of HCV among HIV infected GBM increased in the first decade of the 2000s and although there are variations between countries, the midpoint prevalence is currently approximately 6.4% [1]. Despite high reinfection rates following successful HCV treatment in GBM, modelling suggests that scaling up DAA treatment to need would result in considerable reductions in HCV burden in this group [7, 15]. However, ongoing monitoring of HCV-related risk behaviors is required because these reductions could be offset by an increasing pool of GBM engaging in high risk behaviors and additional behavioral interventions may be required [15]. Preliminary results from studies of GBM who have received DAA treatment indicate that treatment scale-up is possible within clinic-recruited cohorts of HIV-infected GBM [83, 84, 97, 98]. However, these studies are of GBM in HIV care, and do not account for those who remain undiagnosed or who are not regularly accessing HIV care. Ongoing monitoring is required to determine whether these increases in HCV treatment uptake will lead to sustained reductions in HCV prevalence and incidence, including reinfection incidence. Additional interventions to prevent HCV and along the HCV care cascade may be required and these should be evaluated rigorously so that successful interventions can be broadly adopted. Research is also required to measure HCV prevalence in HIV infected GBM in other parts of the world, particularly in central Asia, Eastern Europe and Sub-Saharan Africa where the burden of HCV/HIV coinfection is high in other population groups.

13. Expert Commentary

The introduction of interferon-free DAA therapy has raised the prospect of HCV elimination. Whereas global HCV elimination may be ambitious, micro-elimination in HIV infected GBM seems more feasible, particularly in high-income countries. HIV-infected gay and bisexual men are already linked to regular medical care for HIV treatment in increasingly high numbers which may assist with linkage to HCV care. In high-income countries, the HCV epidemic is well characterized in this group and there are signs that HCV treatment uptake is increasing, making the possibility of HCV micro-elimination in GBM particularly encouraging. Moreover, early data on SVR rates in the DAA era have been very promising.

Nonetheless, in order to achieve HCV elimination in HIV-infected GBM, early increases in treatment will not be sufficient unless increases in treatment uptake can be sustained into the future. In order to sustain current treatment rates, additional interventions at the behavioral, physician, and structural levels may be required to increase HCV diagnosis, including prompt detection of HCV reinfection.

Research from the interferon-era suggest that reinfection after successful HCV treatment is relatively common in GBM, highlighting the importance of post-treatment monitoring. Current standard of care often does not include regular HCV RNA testing after treatment, limiting the possibility for reinfection cases to be detected promptly and re-treated. Research is required to identify sub-groups at elevated risk of HCV reinfection and determine optimal HCV RNA testing intervals, across different settings. In order to maximize the population-level impact of HCV DAA therapy, interventions to maximize detection of infections (including re-infections) and treatment delivery, and ongoing monitoring of primary infection and re-infection should be considered.

Further potential challenges include transmission between GBM from different countries and transmission between HIV-infected and HIV-uninfected GBM. There is currently no clear evidence of transmission between GBM and other risk groups but further research is required to assess whether GBM are at risk of acquiring HCV from other groups in some contexts.

14. ***Five-year view***

In five years, we will be in a position to assess:

- Trends in HCV treatment uptake among co-infected GBM, including trajectories beyond the first year of DAA access; and
- Trends in HCV prevalence and incidence among co-infected GBM, including HCV reinfection incidence after the introduction of DAA therapy.

Within five years, some jurisdictions may have effectively treated all those GBM who have been diagnosed with HIV/HCV coinfection in their region, ostensibly achieving 'micro-elimination'. Ongoing surveillance may offer clues as to whether this will be sustainable. If HCV treatment uptake can be sustained at high levels, we expect HCV prevalence and primary infection incidence to decrease among GBM in high-income countries. There are likely to be increases in HCV reinfection incidence in the short-term followed by decreases as HCV prevalence decreases.

15. Key issues:

- In the absence of DAA therapy, HIV-coinfected patients are less likely to spontaneously clear HCV and are at increased risk of long-term sequelae including liver-related mortality. Nonetheless, DAA therapy is equally effective in HIV-coinfected patients as in HCV mono-infected patients
- The introduction of broad access to DAA therapy provides an opportunity to reduce HCV prevalence and incidence in HIV-coinfected GBM. In high-income countries, high rates of HIV diagnosis and ART treatment, as well as knowledge of HCV coinfection prevalence and incidence, make the prospect of HCV elimination in this population particularly encouraging.
- Early data from the DAA era suggest that treatment uptake is increasing, and SVR rates are very promising. However, current estimates of treatment uptake are among those in HIV care, and it is not clear whether additional interventions will be required to reach those not diagnosed and/or not in care.
- Potential challenges to HCV elimination in HIV infected GBM include reinfection after treatment, transmission between HIV infected and uninfected GBM, and transmission between GBM and other risk groups.
- Additional research is required to measure the HCV burden in GBM in several regions where this is currently unknown in order to determine whether targeted HCV elimination programs for GBM are warranted.
- Existing HIV cohorts provide a useful platform to monitor HCV elimination activities.

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Reference annotations

* Of interest

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