Modifiable risk factors for Hepatitis C virus coinfection among HIV-positive men who have sex men at Île-de-France: need for innovative harm reduction micro-elimination strategies (ANRS 9520 DRIVER)

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Abstract

Background

Since the last decade, prevalence of hepatitis C virus (HCV)-infection has increased among human immunodeficiency virus (HIV)-positive men who have sex with men (MSM). We aimed to assess the prevalence of HCV coinfection in HIV-positive MSM and identify associated factors in Île-de-France

Method

This was a multicentric study conducted among HIV-positive MSM seen at least once between 2015 and 2017 HIV clinics of Ile-de-France. Clinical data using CRF, sociodemographic and behavioral data including sexual practices using self-administered questionnaire were collected. All the participants were screened for viral hepatitis including HCV infection. Multivariable logistic regression was used to identify factors associated with HCV co-infection

Result

In this study, 781 HIV-positive MSM were included with a mean age of 46.76 years (Standard Deviation [SD] = 10.94) and the mean time since HIV diagnosis was 13.93 ± 9.43 years. Of them, 77 participants were infected with HCV with a prevalence of 9.9%; (95% confidence intervals (CI) 7.9% – 12.2%). In multivariable analysis, after adjustment for time since HIV diagnosis and history of anal proctitis, history of GHB (aOR 3.53 [95%CI] [1.89;6.58], p < 0.001) or amphetamine (4.72 [2.05;10.85], p < 0.001) consumption, active syphilis infection (3.22 [1.08;9.54], p = 0.035), sensation seeking behavior (“My sexual partners must think that I’m a risk taker” (1.90 [1.04;3.48], p = 0.037)) and risk behavior at sexual intercourses in group ([2.01 [1.05;3.82], p = 0.034) were shown to have significant effect on HCV acquisition.

Conclusion:

This showed high prevalence of HCV infection among HIV-positive MSM in Île-de-France, suggesting the need for not only systematic screening for HCV, but also for a HCV micro-elimination among this vulnerable subgroup.

Background

Around 2.3 million people living with the hepatitis C virus (HCV) worldwide are also infected with the Human Immunodeficiency Virus (HIV) [1]. It is established that HCV infection is more prevalent among HIV-positive individuals than HIV-negative ones [2–4]. In a systematic review of 38 cross-sectional studies, Jin et al [2] found higher prevalence of HCV infection in HIV-positive men (8.3%) than in HIV-

negative men (1.5%). Indeed, HCV and HIV share similar transmission mechanisms, including transmission through blood and to a lesser extent sexual transmission. In France, the prevalence of HCV infection among people living with HIV was estimated in 2015 to be 15.2% [5]. This prevalence varies according to the mode of transmission, and is high among injecting drug users and men who have sex with men (MSM) [6–8]. In the last decade, several studies showed increasing trends of HCV infection among HIV-positive MSM in Asia–pacific region [9, 10], in United States [11] and in Europe [12–14]. In France, data from a large cohort of people living with HIV (PLWH), Dat'AIDS, showed an increased incidence of HCV infection among HIV-positive MSM, from 0.43% person-years in 2012 to 1.11% person - years in 2016 [15].

Several studies [17–19] evidenced factors that may contribute to the high incidence and prevalence of HCV among HIV-positive MSM (compared to other populations), including high prevalence of coexistent sexually transmitted infections (STIs) unprotected sexual behaviors, high numbers of sex partners, use of drugs during sex (chemsex), traumatic sexual practices, such as the use of sex toys and fisting.

Thanks to preventive interventions aimed at reducing the risk of infection among people who inject drugs [20], and test and treat strategies expanded access to direct-acting antiviral agents (DAA) also for key populations [21], overall prevalence of HIV-HCV coinfection has significantly declined [7, 22]. Therefore, the persistence and spread of HCV infection observed among MSM may suggest outbreaks of sexually transmitted HCV, particularly among HIV-positive MSM [23, 24].

In addition, higher rates of HCV reinfection after successful treatment and cure in HIV-positive MSM have been reported [25–27], due mainly to the persistence of risk behaviors. In a retrospective analysis in HIV infected MSM included in the NEAT (European AIDS Treatment Network) Ingiliz et al [28] found that a quarter of them (24.6%) presented a HCV reinfection. Though frequent HCV testing (and treatment) are an interesting strategies in MSM [21], the influence of some modifiable risk factors, including chemsex could disproportionately affect this re-infection risk [29].

Indeed chemsex involves the use of drugs before or during sex, including mostly mephedrone, methamphetamine, cocaine, ketamine and GHB (Gamma hydroxybutyrate), leading to physical and mental health harms, high risk behaviours in MSM that could increase transmission risk of blood borne viruses and sexually transmitted infections (STIs) in that group [30, 31]. Harm reduction strategies are increasingly being offered among MSM for control the spread of epidemic infections such as viral hepatitis [30].

In this context, it appears necessary to understand the estimate the relative weight of modifiable behavioral risk factors with respect to clinical factors in order to suggest novel interventions to be combined with test and treat strategies. This study, we aimed to assess the prevalence of HCV coinfection in HIV-positive MSM and identify modifiable factors associated with HCV coinfection in a high HCV prevalent area (Ile de France).

Methods

Study design

The French ANRS 9520 DRIVER was a prospective cross-sectional study among HIV-positive men who have sex with men (MSM), followed up biannually in seventeen HIV clinics in Île-de-France. The participants were included in a first period in 2015 for 8 months and in a second period in 2017 for 6 months. It was expected to recruit 500 and 300 participants during the both periods respectively. In the first recruitment period, the questionnaire and questions were reviewed and only the relevant questions retained for the second period. All HIV-positive MSM patients aged between 18 and 75 years old, who agreed to participate in the cohort and did not report any clinical symptoms or treatment for STI the day of the study, were included in this study after providing written informed consent. A French Ethics Committee approved the study (IDRCB 2014-A01362-45), and it was also registered on ClinicalTrials.gov with ID: NCT02413632.

From the participants included in this study, clinical and biological data, history of genital, anal or oro-pharyngeal STIs were collected. Laboratory analysis was performed to investigate genital, anal or oro-pharyngeal ASTI including syphilis chlamydia and gonorrhea infections (screening by PCR). Participants last HCV-antibody and HBV serology were collected from the patient's files. Participants completed also self-administered questionnaire, which collected patients' sociodemographic characteristics and data on behavioral, sexual practices information and STIs' knowledge.

Variables definition

In this study, our main outcome variable was HCV co-infection defined as presence of HCV-antibodies.

Explanatory variables

Clinical and biological variables: time since HIV diagnosis, duration of antiretroviral treatment initiation, co-infections with HBV or HCV, detectable HIV viral load (≥ 50 copies/ml) and CD4 cell count (<500cells/mm^3 vs ≥500cells/mm^3), and history of syphilis, history of chlamydia, history of gonorrhea were included in this analysis.

Sociodemographic variables: age educational level (high school graduate, yes vs no), family status, living in couple (yes vs no), and employment status (being employed, yes vs no).

Behavioral variables included drugs consumption such as cannabis, heroin, GHB, amphetamine and poppers, and Viagra consumption during the last 6 months with yes vs no answer. Sexual sensations seeking and the compulsive sexual behavior were explored using Zukerman' scale (with 40 items).

Sexual practices during the last 6 months : number of sexual partners (categorized in "None", "1-5" and "More than 6"), having gave or received money (or drugs) for sexual intercourses (yes vs no), condom use during anal penetrations and oro-genital practices (yes vs no), stable and casual relationships with last

HIV status of partner (yes vs no), protected sexual intercourses for anal penetrations and oro-genital practices with stable and last casual partner, and the meeting place of casual partners (venue or electronic media) during the last 6 months with yes vs no answer.

Statistical analysis

Sociodemographic and clinical and behavioral characteristics of the participants were described using absolute frequencies, proportions for categorical variables, or means and standard deviation (SD) for continuous variables. We used binary logistic regression models to identify factors associated with HCV co-infection. In the univariate analysis, we identified explanatory variables correlated with HCV co-infection. Those with a liberal p-value ≤ 0.25 were selected to be candidates for the final multivariable model by taking into account potential correlations between variables. The final multivariable model was built using a backward selection procedure, which was based on the likelihood ratio test ($p < 0.05$). Results were reported as adjusted odds ratios (aOR) with 95% confidence intervals (CI). Statistical analyses were performed using STATA software, version 14.2 (StataCorp LLC, USA).

Results

Participants' characteristics

In the study 781 HIV-positive MSM were included. Their mean age was 46.8 ± 10.9 years, 81.1% of them had high school graduate, 39.0% were living in a couple, 77.6% were employed. The mean time since HIV diagnosis was 13.9 ± 9.4 years (Table 1). Almost all patients (93.2%) had undetectable HIV viral load (< 50 copies/ml). The mean CD4 cell counts was 709 ± 298 /mm^3 and more than three-quarter of the participants had more than 500/mm^3. More than 75% of the participants had at least one history of STI (43.7% of syphilis, 32.9% of condyloma, 20.7% of gonorrhea and 11.3% of chlamydia) and 13.2% had asymptomatic STI screening (4.2% of syphilis, 7.6% of chlamydia and 6.8% of gonorrhea). Almost 10% of the participants were co-infected with HCV (resp. 4.1% with HBV).

Table 1
Factors associated with HCV co-infection: univariate binary logistic regression (N = 781 patients)

N = 781	**n(%) or mean ± SD**	**Univariate**		**Multivariate**	
		OR [95% CI]	**p-value**	**aOR [95% CI]**	**p-value**
Sociodemographic characteristics					
Age (years)	46.8 ± 10.9	1.01 [0.98;1.03]	0.619		
High school graduate (ref: No)	625 (81.1)	0.79 [0.45;1.41]	0.429		
Living in a couple (ref: No)	303 (39.0)	0.94 [0.58;1.52]	0.797		
Being employed (ref: No)	601 (77.6)	0.80 [0.47;1.38]	0.430		
Clinical characteristics					
CD4 > 500**/mm^3** (ref:< 500/mm^3)	602 (77.1)	0.98 [0.56;1.70]	0.930		
Time since HIV diagnosis (years)	13.9 ± 9.4	1.04 [1.02;1.07]	**0.001**	1.08 [1.05;1.12]	**< 0.001**
Undetectable HIV viral load level* (ref: No)	728 (93.2)	6.08 [0.83;44.61]	0.076		
History of anal proctitis (ref: No)	84 (10.8)	3.50 [1.98;6.19]	**< 0.001**	3.47 [1.74;6.91]	**< 0.001**
History of condyloma (ref: No)	257 (32.9)	1.34|0.83;2.18]	0.231		
At least one history of STI (ref: No)	592 (75.8)	1.65 [0.89;3.06]	0.115		
Syphilis positive (ref: No)	33 (4.2)	3.74 [1.67;8.37]	**0.007**	3.22 [1.08;9.54]	**0.035**
Positive test of asymptomatic STI (ref: No)	103 (13.2)	1.69 [0.92;3.09]	0.092		
Co-infected with HBV (ref: No)	32 (4.1)	1.74 [0.65;4.65]	0.272		
Co-infected with HCV (ref: No)	77 (9.9)				

* (< 50 copies/ml)

[1] During the last 6 months

N = 781	n(%) or mean ± SD	Univariate		Multivariate	
		OR [95% CI]	p-value	aOR [95% CI]	p-value
Behavioral characteristics					
Recent use of cannabis consumption (ref: No)	172 (22.3)	2.35 [1.40;3.96]	**0.001**		
Recent use of GHB consumption (ref: No)	58 (7.6)	4.15 [2.54;6.79]	**< 0.001**	3.53 [1.89;6.58]	**< 0.001**
Recent use of amphetamine consumption (ref: No)	22 (2.9)	8.36 [4.24;16.48]	**< 0.001**	4.72 [2.05;10.85]	**< 0.001**
Recent use of poppers consumption (ref: No)	291 (38.2)	2.80 [1.56;5.03]	**0.001**		
Recent use of Viagra consumption (ref: No)	131 (17.1)	2.69 [1.66;4.34]	**< 0.001**		
"My sexual partners must think that I'm a risk taker" (ref: No)	303 (40.1)	2.88 [1.75;4.73]	**< 0.001**	1.90 [1.04;3.48]	**0.037**
"I like sensations taking by non-condom sexual intercourse" (ref: No)	481 (64.5)	2.94 [1.55;5.58]	**0.001**		
Sexual practices characteristics					
Number of sexual partners[1]	110 (14.3)	1	0.958		
None	380 (49.4)	0.98 [0.43;2.22]	0.071		
1–5	279 (36.3)	2.08 [0.94;4.61]			
More than 5					
Stable relationship[1] (ref: No)	423 (55.1)	0.95 [0.59;1.54]	0.840		
Casual partners[1] (ref: No)	521 (68.4)	1.77 [0.99;3.15]	0.052		
Have gave or received money (or drugs) for sexual intercourses[1] (ref: No)	51 (6.6)	1.02 [0.39;2.66]	0.961		
Inconsistent condom use during anal penetrations[1] (ref: No)	334 (43.8)	2.02 [1.24;3.29]	**0.005**		

* (< 50 copies/ml)

[1] During the last 6 months

N = 781	n(%) or mean ± SD	Univariate		Multivariate	
		OR [95% CI]	p-value	aOR [95% CI]	p-value
Inconsistent condom use during oro-genital practices[1] (ref: No)	172 (22.8)	0.84 [0.47;1.53]	0.575		
Risk at sexual intercourse with stable partner for anal penetration[1] (ref: No or not concerned)	129 (16.8)	1.54 [0.87;2.75]	0.141		
Risk at sexual intercourse with stable partner for oro-genital practices[1] (ref: No or not concerned)	167 (21.7)	1.48 [0.87;2.54]	0.151		
Risk at last sexual intercourse with casual partner for anal penetration (ref: No or not concerned)	198 (25.5)	2.64 [1.63;4.29]	**< 0.001**		
Risk at last sexual intercourse with casual partner for oro-genital practices (ref: No or not concerned)	384 (49.4)	2.42 [1.46;4.01]	**0.001**		
Risk at sexual intercourses in group[1] (ref: No or not concerned)	119 (16.3)	4.56 [2.71;7.66]	**< 0.001**	2.01 [1.05;3.82]	**0.034**
* (< 50 copies/ml)					
[1] During the last 6 months					

Regarding behavioral and sexual practices, patients reported recent use of drugs, including poppers (38.2%), cannabis (22.3%), GHB (7.6%) and amphetamine (2.9%) and Viagra (sildenafil) (17.1%). Sensation seeking behaviors such as “My sexual partners must think that I’m a risk taker” and “I like sensations taking by non-condom sexual intercourse” were also reported in 40.1% and 64.5% of the participants. During the six previous months, 36.3% of the participants reported more than 5 sexual partners and 6.6% were engaged in transactional sex. More than half of the patients (55.1%) had stable relationship and 68.4% had casual partners. Inconsistent condom use during anal sex and oro-genital sexual practices was reported respectively in 43.8% and 22.8% of the participants. In addition, 16.3% of the participants reported risk behavior during sexual intercourses in group (Table 1).

Associated Factors With Hcv Co-infection

In the univariate analysis, time since HIV diagnosis, history of anal proctitis, syphilis infection, recent drug consumption (cannabis, heroin, GHB, substitution treatment, amphetamine, poppers) and Viagra,, sensation seeking behaviors (including “My sexual partners must think that I’m a risk taker”, “I like sensations taking by non-condom sexual intercourse”) were also significantly associated with HCV co-

infection. During the last 6 months, patients who reported inconsistent condom use during anal sex, those having reported risk at sex in-group were also associated with HCV co-infection. However, sociodemographic characteristics and inconsistent condom use for oro-genital sex were not associated with HCV co-infection (Table 1).

In multivariable analysis, after adjustment for time since HIV diagnosis, history of anal proctitis, HIV-positive MSM with recent amphetamine (aOR, 4.72; 95%CI, 2.05;10.85; p < 0.001) or GHB (aOR, 3.53; 95%CI, 1.89;6.58; p < 0.001) use, those who were tested positive for syphilis (aOR, 3.22; 95%CI, 1.08;9.54; p = 0.035), those who reported risk behavior at sexual intercourses in group (aOR, 2.01; 95%CI, 1.05;3.8; p = 0.034) and those who reported sensation seeking behavior “sexual partners must think that I’m a risk taker” (aOR, 1.90; 95%CI, 1.04;3.48; p = 0.037) were more likely to be infected with HCV.

As logistic regression is a multiplicative model, this means that those reporting both GHB and amphetamine use exhibit a 4.72x3.53 = 16.7 increased risk of HCV acquisition.

Discussion

In this prospective and multicentric study of HIV-positive MSM who were followed-up in HIV clinics in Île-de-France, we highlighted that 1 out of 10 HIV-positive MSM was also coinfected with HCV. This prevalence is much higher than the estimated prevalence found in HIV-positive MSM in the cross-sectional survey PREVAGAY in 2015 in France (3%) [4], but lower than that reported in HIV-positive MSM in the Dat’AIDS cohort in 2016 in France [15]. However this lower prevalence in the French PREVAGAY study might due to the use of DBS for HCV antibodies detection, which could lead to an underestimation of HCV prevalence [32, 33], but also to the younger age of the participants. Nevertheless the prevalence of HCV infection found remains comparable to those reported among HIV-positive MSM in Amsterdam (11.8%) [34] and in a meta-analysis of international observational studies among HIV-infected MSM (8.1%) [19].

The main result of the study is the identification of two main modifiable risk factors (in terms of strength of association), i.e. recent GHB or amphetamine use. In the univariate analysis amphetamine users exhibit the highest risk (8-fold) of HCV acquisition. Due to the confounding and overlapping of some risk factors, this association decreases in the multivariate analysis though it remains the strongest association with the outcome in the final model.

Comparable findings were reported in Montréal [35] and in Thailand [36]. In fact, GHB or stimulants are used during sex in MSM to decrease inhibition, which favor risky behaviors for HCV acquisition such as syringes or needles exchange, increasing number of sexual partners and condomless receptive anal intercourse. Whatever the administration route (rectally, orally or intra-nasally), these substances may favor contact with partner or fellow user’s secretions or blood, where HCV could replicate [37]. It was also well documented that HIV-positive MSM who reported amphetamine-type substance use reported also group sex, associated with risky behaviors [17, 36]. This probably explains why this variable in the model decreases the association between amphetamine use and HCV acquisition. The association with group

sex is in line with our study; in which reporting risk practices during group sex was a strong predictor of HCV seropositivity among HIV-positive MSM. Group sex participation might be associated with other risk sexual practices such as unprotected fisting (without gloves), sharing sex toys or condomless receptive anal sex that could cause mucosal tissue traumatism and rectal bleeding, facilitating thus HCV infection [17].

Our findings showed that HIV-positive MSM who reported seeking sensation, including sexual sensation were more likely to have HCV infection, particularly those who declared: “My sexual partners must think that I’m a risk taker”. It was also demonstrated that in sexual minority individuals high seeking sensation might encourage them to be engaged in intentional unsafe sex most often mediated by alcohol use or drug use before sex [38, 39], with an increased risk of HCV infection.

Our study also showed that HIV-positive MSM with active syphilis infection or history of anal proctitis were more likely to be infected with HCV. Similar to previous studies [17, 40, 41], active the presence syphilis infection with an anorectal or oral chancre and other ulcerative STI, including lymphogranuloma venereum, might increase the risk of transmission HCV infection among HIV-positive MSM, as these lesions could serve as a portal of entry for HCV [17].

Our findings suggested the high burden of HCV and HIV coinfection among MSM in Île-de-France, hence the need to strengthen interventions for micro-elimination but also the implementation of harm reduction strategies (especially among drug users) for HCV eradication among this core group. Since 2016, universal access to DAA announced by the French Ministry of Health [42], access to DAA-based treatment for HCV infection has been extended to all patients with active HCV-infection, regardless of their profile or the stage of liver disease. This may greatly change the course HCV epidemic among HIV-positive MSM. In the context of high rate of HCV screening, modelling data demonstrated that by increasing treatment coverage, DAA could favor HCV infection elimination in MSM, even in the most highest group, including intra-venous drug users [45]. Recently, the European treatment Network for HIV, Hepatitis and Global Infectious Diseases (NEAT-ID) consensus panel recommend immediate HCV treatment after diagnosis in HIV-positive MSM in order to prevent HCV transmission [46]. An encouraging study conducted in the French large Dat’AIDS cohort of HIV-positive patients has shown that the majority (82%) of patients with HCV and HIV coinfection including MSM were treated and cured for HCV infection [15]. Given the high prevalence and persistence of HCV infection, HIV-positive MSM are considered as one of main targets and a priority population for of HCV micro-elimination.

Furthermore, in HIV-positive MSM remained at increased risk of HCV reinfection, due to their engagement in high-risk behaviors, particularly in those who reported intravenous drug use [47]. Harm reduction strategies, assuming needle and syringe provision and supervised drug injection or opioid substitution treatment, may be effective and promote safe drug injecting practices [48]. In a harm-reduction program implemented in Australia for methamphetamine users MSM, authors found significant change in participants’ behaviors in terms of sexual risk behavior and high risk drug use behavior, including reductions in methamphetamine use post intervention [49]. Therefore, the scale-up of screening for HCV,

HCV treatment and prevention interventions, harm reduction interventions, including safe behaviors, should be needed to minimize the risk of HCV re-infection in this vulnerable group.

Our study has some limitations. This study was conducted among HIV-positive MSM followed up in HIV clinics in Île-de-France. Therefore, the sample may not be representative of the whole country. In addition, it was likely to include a high proportion of HIV-positive MSM with better prevention behaviors or HIV-positive MSM less infected with HCV. Some behavioral data, including sexual behavior and drug use based on self-reports may have been affected by social desirability bias (underreporting of drug use or history of drug use, for example). This study did not assess HCV reinfections in HIV-positive MSM and that could contribute to a misclassification of participants in high groups.

Conclusion

This multicentric study highlighted high prevalence of HCV infection among HIV-positive MSM in Île-de-France. The major impact of modifiable risk factors such as amphetamine and GHB suggest that innovative harm reduction strategies need to be tested in this population together with HCV test and treat approaches to reach micro-elimination among MSM at higher risk of re-infections.

Declarations

Authors' contribution

MD, SD, OC and DZ designed and coordinated the ANRS DRIVER study. EF , PdT and MK contributed to the participant recruitment and data collection. MPC and IY contributed to data analysis and results interpretation. IY drafted the manuscript. All the authors reviewed and approved the manuscript.

Competing interests

No authors report any conflict of interest in relation with the study.

Ethics approval

Ethical considerations reviewed and approved by a French Ethics Committee approved the study (IDRCB 2014-A01362-45).

Consent to participate

Written informed consent was obtained from all individual participants included in the study.

Data Availability statement

Data are available from the first and corresponding author on reasonable request.

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