Hepatitis C virus infection in HIV-infected men who have sex with men: sustained rising incidence in Antwerp, Belgium, 2001–2009

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During the last decade, outbreaks of acute hepatitis C virus (HCV) infection have been reported among human immunodeficiency virus (HIV)-infected men who have sex with men (MSM) in several European countries. To study this emerging infection in MSM in Antwerp, Belgium, we reviewed all cases of newly acquired HCV infection in HIV-positive MSM followed from 2001 to 2009 at the HIV/sexually transmitted infection (STI) reference clinic of the Institute of Tropical Medicine in Antwerp. Newly acquired HCV infection was considered as certain or probable according to local definitions. During the study period, 69 episodes of newly acquired HCV infection (40 certain and 29 probable) were diagnosed in 67 HIV-infected MSM. In only 10 episodes (14%) were the patients symptomatic. The annual incidence of HCV infection in our population of HIV-infected MSM rose steadily from 0.2% in 2001 to 1.51% in 2008, and then peaked to 2.9% in 2009. For 60 episodes (87%), another STI (mainly syphilis and lymphogranuloma venereum) had been diagnosed within the six months before the diagnosis of HCV infection. All but one patient with available genotyping (n=54) were found to be infected with the difficult-to-treat HCV genotypes 1 or 4. Our results therefore demonstrate the rising incidence of HCV infection in HIV-positive MSM in Antwerp, since 2001, which reached an alarming level in 2009. Targeted awareness campaigns and routine screening are urgently needed to limit further HCV spread and its expected long-term consequences.

Introduction

Since 2000, the prevalence and incidence of hepatitis C virus (HCV) infections have increased in human immunodeficiency virus (HIV)-infected men who have sex with men (MSM) in large cities in the Netherlands [1], United Kingdom [2], France [3], the United States [4] and Australia [5]. Although sexual transmission of HCV is known to be rather inefficient in discordant heterosexual couples, recent observations suggest that this is the most likely mode of HCV acquisition among HIV-infected MSM [1,6-8]. High prevalence of ulcerative sexually transmitted infections (STIs), mainly syphilis and lymphogranuloma venereum (LGV), has been reported in HIV/HCV co-infected MSM [9,10] suggesting that HCV infections among MSM epidemiologically follow the epidemics of syphilis (observed since the beginning of 2000 [11-13]), and of LGV (which emerged a few years later) [14-16]. Recently, rough sexual techniques such as fisting and use of recreational drugs, in particular gamma hydroxyl butyrate (GHB), have been identified as independent risk factors for HCV transmission in MSM, beside intravenous drug use (IDU) and HIV infection [1,7,17]. In addition, phylogenetic analyses have revealed a high degree of HCV clustering among HIV/HCV co-infected MSM in Amsterdam, the Netherlands [1,7] and the existence of a large, international network of HCV transmission in HIV-positive MSM has been demonstrated in several European countries [18].

Hepatitis C is therefore increasingly perceived as an emerging and expanding STI in HIV-infected MSM. It is well known that the clinical management of HIV/HCV co-infection is complex [6] and poses specific epidemiological challenges [7,8], hence the importance of surveying the incidence and prevalence of HCV infection in this specific group. The main purpose of this study was to quantify the rising number of new HCV infections in HIV-infected MSM in the HIV/STI reference clinic of the Institute of Tropical Medicine, Antwerp, Belgium, over the past decade. A second objective was to document the current management and clinical outcome of these co-infected patients.

Methods

A retrospective study was conducted at the reference HIV/STI clinic of the Institute of Tropical Medicine in Antwerp. By the end of 2009, 1,844 HIV-positive individuals had been actively followed up in our clinic (in 2001, there were 914). Some 70% of these were men; half of them had acquired their HIV infection through homo- or bisexual contacts. For this study, we reviewed the records of all HIV-infected MSM who had been

diagnosed with a newly acquired HCV infection from January 2001 to December 2009.

The standard HIV management during the study period was as follows: HIV-positive individuals were seen by a physician and screened for HIV-related co-infections (including viral hepatitis) at the first consultation in our clinic. They were seen thereafter every three to four months for routine clinical HIV care and for laboratory measurements, including regular determination of the CD4 cell count, the HIV RNA load, and level of liver alanine aminotransferase and aspartate aminotransferase. Additional consultations were possible at any time between routine visits for any health problem including suspicion of another STI. Patients with a negative HCV serological result at the initial HIV consultation were re-tested for HCV if there was a subsequent increase in the level of liver aminotransferases. Since 2005, (because of ongoing HCV outbreaks in neighbouring countries), HIV-infected MSM attending our clinic were also systematically tested for HCV after each STI episode or after sexual contact with an HCV-infected partner, even if the level of liver aminotransferases was normal. Also, those considered by the treating physician as being at high risk for HCV infection (for example, those with multiple sexual partners, GHB users and frequent visitors to known high-risk discotheques or saunas) were tested at least once a year for HCV.

Hepatitis C virus tests

The HCV test used for serological screening throughout the study period was Vitros ECI Immunodiagnostic System (Ortho Clinical Diagnostics) and the confirmatory serological test was INNO-Line Immuno Assay HCV Score (Innogenetics). When the confirmatory serological test was positive, molecular qualitative detection of HCV RNA was performed using COBAS Amplicor HCV test, version 2.0 (Roche Diagnostics), with a detection limit of 50 IU/mL. If genetic material (HCV RNA) was detected by qualitative testing, it was then quantified by reverse transcription polymerase chain reaction, using the COBAS Amplicor HCV Monitor Test, version 2.0 (Roche Diagnostics), with a detection limit of 600 IU/mL). Since November 2006, qualitative as well as quantitative molecular HCV RNA testing was performed using Abbott RealTime HCV assay. If molecular testing was positive, viral genotyping was performed by line probe assay: up to 2006, INNO-LiPA (Innogenetics) was used; since 2006, Versant HCV genotype 2.0 assay LiPA (Siemens) According to the manufacturer, genotyping was expected to be successful in 95% of samples with HCV RNA levels greater than 1,000 IU/mL.

Definitions of newly acquired HCV infection

We defined an episode of newly acquired HCV infection as certain if HCV-antibody seroconversion could be documented, that is, a screening serological test and a confirmatory serological test were positive, and the screening test had been negative in the previous 24 months. A newly acquired HCV infection was considered as probable if both the screening and confirmatory serological tests were positive and aminotransferase levels were elevated, with exclusion of other causes of hepatitis, in a person with a negative serological test documented longer ago than the previous 24 months. This limit of 24 months was chosen pragmatically in this study for diagnosing a recent HCV infection, since HCV testing was not done systematically in the early phase of the study. However, on the basis of these definitions, we excluded patients newly diagnosed simultaneously with HIV and HCV infections and patients who had never been tested previously for HCV before their HCV diagnosis. In such cases the duration of HCV infection is unknown and we would probably have included a substantial number of chronically infected patients who were not necessarily epidemiologically linked to the increase in HCV infection observed since 2001.

Determination of level of liver aminotransferases

The level of liver aminotransferases was determined on the day of HCV diagnosis. The serum level of the alanine aminotransferase (ALT) enzyme was graded according to the following scale:

- grade 0 – normal value of alanine aminotransferase;
- grade 1 – between the upper limit of normal (ULN) of alanine aminotransferase and 2.5 times the ULN;
- grade 2 – between 2.5 and five times the ULN;
- grade 3 – between five and 10 times the ULN;
- grade 4 – more than 10 times the ULN.

Testing and treatment of patients

Patients diagnosed with newly acquired HCV infections were retested six months later to determine whether they remained chronically infected (presence of HCV RNA persisting after six months). In such cases, liver biopsy was systematically offered according to the current standard of care in Belgium for HIV patients chronically infected with HCV. All patients with viral or histological criteria for therapy were offered standard combination treatment of pegylated interferon and ribavirin for one year.

Incidence calculations

To calculate the annual incidence of reported newly acquired HCV infection, the total number of episodes diagnosed each year (certain and probable infections) was divided by the mean of the number of HIV-infected MSM actively followed at the beginning and at the end of the relevant year.

Associated sexually transmitted infections

An STI was considered as associated with the newly acquired HCV infection when it had been diagnosed within six months before the diagnosis of HCV infection. STIs were diagnosed by culture or molecular demonstration of pathogens in relevant fluids or secretions, or by unequivocal serological results (seroconversion or single high antibody titre against *Treponema pallidum* and/or *Chlamydia trachomatis*) in a suggestive clinical context.

Results

A total of 69 episodes of newly acquired HCV infection (40 certain, 29 probable) were retrospectively diagnosed in 67 HIV-infected MSM from 2001 to 2009 (Table 1). Two patients had a second HCV infection after documented spontaneous clearance of the virus. Two of the 67 patients reported intravenous drug use. The origin of all but four patients was a European country (mostly Belgium, n=59). The mean age of the patients was 41 years (range: 21–58 years). The median duration of HIV infection before HCV diagnosis was 47 months (range: 1–211 months). At HCV diagnosis, the median CD4 cell count was 508/µL (range: 13–1,355); 56 patients were undergoing antiretroviral therapy and 51 of them had a level of HIV RNA below 400 copies/mL (with no significant differences between certain and probable episodes). Eight of the 67 patients had also chronic hepatitis B. Of note, an additional 11 HCV infections, although clinically very suspect, were not included because recent HCV acquisition could not be ascertained (as no anti-HCV screening had been available before the HCV diagnosis).

The annual incidence of reported newly acquired HCV infection (confirmed and probable) among the HIV-infected MSM is shown in Figure 1. The incidence rose from 0.2% (0.2 infections per 100 HIV-infected MSM) in 2001 to 2.9% in 2009 and doubled from 2008 to 2009. When considering confirmed infections only, the incidence rose from 0% in 2001 to 2.3% in 2009. For the patients with certain newly acquired HCV infection, the median interval between last negative HCV serological result and HCV diagnosis was nine months (range: 3–24); for the patients with probable newly acquired HCV infection, the median interval was 32 months (range: 25–61).

As shown in Table 2, HCV testing was performed between routine visits in 10 episodes because the patients presented with symptoms: acute jaundice (n=5), severe asthenia (n=3) and nausea and vomiting (n=2).

Diagnosis of HCV infection was made for 55 asymptomatic episodes because of an increase in the serum level of alanine aminotransferase at a routine visit and in the four remaining episodes without any suggestive clinical or laboratory abnormality through systematic screening because of high-risk behaviour or STI occurrence. At HCV diagnosis, in only a minority of episodes (31; 45%) patients presented with moderate to severe elevation of the serum level of liver alanine aminotransferase (more than five times the ULN).

STIs were documented together with or within the previous six months of the HCV diagnosis in 60 (87%) of all episodes. The STIs diagnosed were syphilis (n=27), LGV (n=18), both syphilis and LGV (n=12), gonorrhoea (n=2) and genital herpes (n=1). Gonococcal infection was present in two additional patients: in one of these patients, it was present together with syphilis, and in the other, together with syphilis and LGV.

Four patients were lost to follow-up before the determination of HCV RNA levels. Seven episodes of HCV infection cleared probably spontaneously (HCV RNA could not be detected despite a positive HCV confirmatory test or disappearance of HCV RNA within six months after RNA had been detected). HCV RNA was still detected more than six months after HCV diagnosis in the remaining 58 episodes (defining a chronic course of infection). Table 3 shows the viral characteristics and outcome data of those 58 who developed chronic HCV infection (as of April 2010). All but one episode with successful genotyping (n=54) were due to genotype 1 or with genotype 4, which are notoriously difficult to treat [6]. In about 70% of chronic infections (n=40), the HCV RNA load was high (greater than 850,000 IU/mL). As of April 2010, 37 patients had undergone a liver biopsy, which revealed moderate to severe fibrosis

Table 1

Annual number of episodes of newly acquired HCV infections (certain and probable) among HIV-infected men who have sex with men[a], Antwerp, Belgium, 2001–2009 (n=69)

Year	Number of HIV-infected MSM[b]	Number of episodes of newly acquired HCV infections diagnosed in HIV-infected MSM		
		Certain	Probable	Total
2001	418	0	1	1
2002	450	0	2	2
2003	508	0	1	1
2004	539	0	3	3
2005	607	2	1	3
2006	686	2	7	9
2007	756	6	4	10
2008	858	9	4	13
2009	922	21	6	27

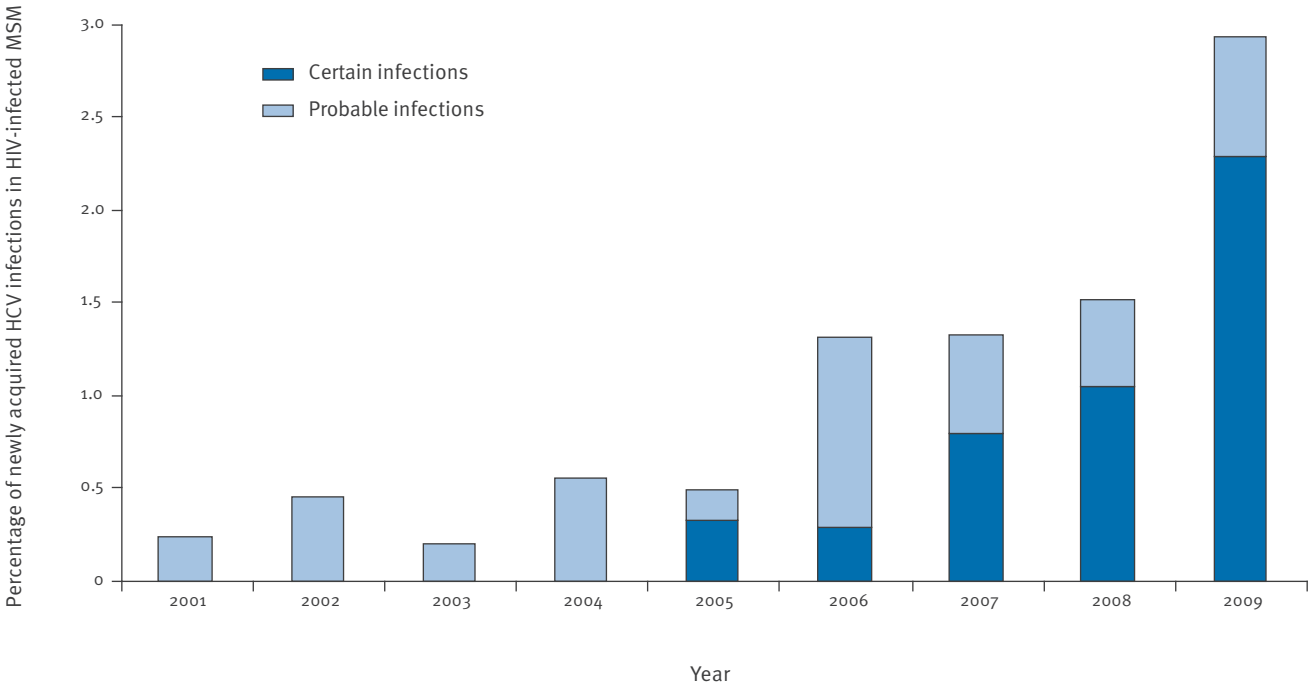
HCV: hepatitis C virus; HIV: human immunodeficiency virus; STI: sexually transmitted infection.

[a] Followed from 2001 to 2009 at the HIV/STI reference clinic of the Institute of Tropical Medicine, Antwerp, Belgium.

[b] Mean value of the numbers of HIV-infected MSM actively followed at the beginning and at the end of each relevant year.

Figure

Annual incidence of episodes of newly acquired HCV infection among HIV-infected men who have sex with men[a], Antwerp, Belgium, 2001–2009 (n=69)



[a] Followed from 2001 to 2009 at the HIV/STI reference clinic of the Institute of Tropical Medicine of Antwerp, Belgium.

Table 2

Clinical features and evolution of episodes of newly acquired HCV infection diagnosed in HIV-infected men who have sex with men[a], Antwerp, Belgium, 2001–2009 (n=69)

Feature or outcome	Newly acquired episodes of HCV infection diagnosed in HIV-infected MSM		
	Certain n=40 Number (percentage)	Probable n=29 Number (percentage)	Total n=69 Number (percentage)
Reason for HCV testing			
Clinical symptoms	5 (13)	5 (17)	10 (14)
Asymptomatic increased level of liver aminotransferases	32 (80)	23 (79)	55 (80)
Exposure to risk	3 (7)	1 (3)	4 (6)
Level of liver alanine aminotransferases at HCV diagnosis			
Grade 0 (normal values)	3 (7)	1 (4)	4 (6)
Grade 1 (between ULN and 2.5 times ULN)	11 (28)	11 (40)	22 (32)
Grade 2 (between 2.5 and 5 times ULN)	7 (18)	2 (17)	12 (17)
Grade 3 (between 5 and 10 times ULN)	9 (22)	7 (24)	16 (23)
Grade 4 (greater than 10 ULN)	10 (25)	5 (17)	15 (22)
Other STIs			
Concomitant or recent STI at HCV diagnosis	35 (87)	25 (86)	60 (87)
Evolution of episodes of HCV infection			
Probable spontaneous HCV clearance	4 (10)	3 (10)	7 (10)
Proven chronic HCV infection	34 (85)	24 (83)	58 (84)
Lost to follow-up	2 (5)	2 (7)	4 (6)

HCV: hepatitis C virus; HIV: human immunodeficiency virus; STI: sexually transmitted infection; ULN: upper limit of normal.

[a] Followed from 2001 to 2009 at the HIV/STI reference clinic of the Institute of Tropical Medicine, Antwerp, Belgium.

(stage F2 or F3 in the METAVIR histological score) in 22 of them, including 12 (56%) of 18 certain infections and 10 (53%) of 19 probable infections. Liver biopsy was performed with a median interval of seven months (range: 3–36 months) after diagnosis of HCV infection, and was refused by many patients.

As of April 2010, 27 of the patients who developed chronic HCV infection have initiated anti-HCV treatment; most (n=22) were undergoing antiretroviral therapy for HIV infection and had a CD4 cell count of greater than 350/µL and an HIV RNA level of less than 400 copies/mL at treatment initiation. The median interval between liver biopsy and the start of HCV treatment was three months (range: 1–12). Sustained viral response to treatment (absence of HCV RNA from serum samples six months after completion of therapy) was observed in only five patients, while one patient stopped treatment because of side effects and eight did not respond (no response after three months' treatment (n=5), no response after six months (n=3)). The remaining 13 patients are still undergoing treatment or follow-up (six months post-treatment). Two patients died, one because of decompensated HCV-related cirrhosis five years after the diagnosis of acute hepatitis C (with no response to treatment) and the other because of non-Hodgkin lymphoma. No difference was observed between certain and probable infections in terms of baseline clinical and laboratory features, viral and histological characteristics, time between liver biopsy and HCV treatment, and outcome data.

Discussion

Over the last decade, we observed a sustained increase in the incidence of hepatitis C in our cohort of HIV-infected MSM. The same trend has also been reported in several HIV clinics of other European cities such as London, Amsterdam and Paris. However, the incidence we observed in 2009 (almost 3% of HIV-infected MSM) is high compared with that reported in other studies [8], suggesting that ongoing HCV transmission has reached a worrying level. In addition, the very high prevalence of other STIs in HIV-infected MSM newly infected with HCV supports the hypothesis that some STIs fuel the HCV epidemic in this population [1,6,17]. The short-term and expected long-term morbidity is of concern, given the very high proportion of patients infected with genotypes 1 and 4, the low rate of spontaneous HCV clearance, the important proportion of high HCV loads (resulting in lower response to treatment), patients' low acceptance rate of liver biopsy and HCV treatment, the sizeable subset of patients with moderate to severe liver fibrosis within a short period of time, as already observed [19] and the disappointing cure rates [20,21].

Our study has the usual limitations of a retrospective single-centre design, that is, it is highly dependent of the quality of data reporting when reporting

Table 3

Characteristics and clinical outcome of HIV-infected men who have sex with men who developed chronic HCV infection[a], Antwerp, Belgium, as of April 2009 (n=58)

Characteristic or clinical outcome	Chronic HCV infections in HIV-infected MSM		
	Certain n=34 Number (percentage)	Probable n=24 Number (percentage)	Total n=58 Number (percentage)
Genotyping			
Unsuccessful	3 (9)	1 (4)	4 (7)
Genotype 1	21 (62)	13 (54)	34 (59)
Genotype 2	1 (3)	0	1 (1.5)
Genotype 4	9 (26)	10 (41)	19 (33)
HCV RNA load			
<850,000 IU/L	11 (32)	7 (29)	18 (31)
≥850,000 IU/L	23 (68)	17 (71)	40 (69)
Liver biopsy			
Performed	18 (53)	19 (79)	37 (64)
Not performed	14 (47)	5 (21)	21 (36)
Clinical outcome			
Death	1 (3)	1 (4)	2 (4)
Not yet treated	17 (50)	12 (50)	29 (50)
Ongoing treatment or follow-up	10 (29)	3 (12)	13 (22)
Treatment stopped (no viral response; dropped out)	5 (15)	4 (17)	9 (16)
Sustained viral response	1 (3)	4 (16.5)	5 (9)

HCV: hepatitis C virus; HIV: human immunodeficiency virus; ULN: upper limit of normal.

[a] Followed from 2001 to 2009 at the HIV/STI reference clinic of the Institute of Tropical Medicine, Antwerp, Belgium.

has not been structured systematically and does not allow immediate generalisation to other settings. Also, periodic HCV screening was not systematically performed throughout the whole study period, nor was the whole MSM population of Antwerp included. It is therefore probable that some HCV infections have been missed and it is also possible that some more chronic HCV infections (without an epidemiological link to the increase of infections observed since 2001) have been included erroneously. However, we used a time-restrictive definition for probable newly acquired infections, and observed that the interval between last negative HCV test and HCV diagnosis did not exceed three years in most episodes of probable infection, This provides some reassurance that these HCV infections were rather recent and were likely to be linked to the increase seen since 2001 (although no definitive molecular proof exists). Also, episodes of certain and probable infection did not differ significantly in terms of clinical, viral, histological features and outcome, suggesting that both groups were similar and the vast majority of the HCV infections were likely to be truly recent. In fact, as mentioned, the actual incidence was probably underestimated during the first years of the study when HCV testing was performed only following clinical suspicion. Numbers reported after 2006 are more likely to reflect the actual incidence because of the much higher proportion of episodes in which there was documented seroconversion, diagnosed through enhanced clinical awareness and more systematic serological testing of patients at risk.

Establishing enhanced surveillance for HCV infection in MSM has been proven feasible [22], although the asymptomatic course of most acute HCV infections strongly complicates case detection. Most of our study participants had no symptoms and were diagnosed after routine consultation when the laboratory reported increased levels of liver aminotransferases in the samples. Also, these liver disturbances were in most episodes very moderate at the time of HCV diagnosis, and might have gone unrecognised in patients with multiple other possible causes of liver enzyme abnormality. This observation questions the accuracy of the 2007 United States Centers for Disease Control and Prevention (CDC) case definition of acute hepatitis C, which includes the presence of jaundice or alanine aminotransferase levels greater than 400 IU/L in addition to serological or molecular confirmation [23]. This case definition is very specific in diagnosing acute HCV infections but, if used as such for surveillance purposes, would miss a substantial number of true acute infections, with serious public health implications. Finally, the small subset of HCV patients with normal levels of liver aminotransferases who were diagnosed through enhanced surveillance underlines the limitation of a surveillance strictly based on laboratory findings. Research should focus on identifying the subset of HIV-infected MSM most in need of intensive follow-up, since costly and repeated molecular testing might become necessary to detect HCV re-infections in high-risk patients who would remain serologically positive even after spontaneous or post-treatment HCV clearance.

The fact that an HIV-positive patient presents with an STI is a sign of ongoing unsafe sexual practices [24]. For more than 25 years, MSM remain the group most affected by HIV and other STIs, and newly diagnosed HIV infections among MSM have been increasing in recent years [12]. Indicators commonly used for monitoring purposes, such as unprotected anal intercourse, condom use, number of sexual partners and HIV testing, all confirm the increase in sexual risk behaviour in MSM in several European countries [24]. Large transmission clusters of HIV infection have been demonstrated in MSM and serosorting – restricting unprotected sexual relations to partners claiming that they have the same (negative or positive) serostatus – which is sometimes used by HIV-negative MSM as a risk reduction strategy, may play a role in HIV transmission. A fraction of MSM who believe themselves to be HIV-negative could in fact be infected since continuous reliance on negative testing results does not adequately address the problem of the highly contagious serological window, for example [24]. Similarly, HIV-infected MSM practicing serosorting may contract HCV infection from each other: HIV infection is by itself a risk factor for HCV acquisition in MSM and HIV/HCV co-infected MSM were often unaware of their HCV serostatus [7]. In addition, the serological window for HCV is often much longer than for HIV. Nevertheless, even if sexual risk behaviour increases in MSM, the specific emergence of HCV infection in the HIV-positive population remains poorly understood. There is probably more involved than sexual transmission alone: blood–blood transmission through rough sexual intercourse or traumatic practices (with shared sex toys or external devices) is another possible route [17]. Gay-friendly Antwerp has some renowned high-risk settings for a particular group of MSM with a risk of further regional and international HCV spread [18]. We think therefore that the detection of hepatitis C in HIV-positive MSM should not only lead to the clinical consideration for HCV therapy, but also to enhanced counselling and specialised support from a psychologist and/or sexologist.

Public health action

Raising awareness and increasing risk perception are the recommended public health actions to limit the spread of viral hepatitis among MSM [7,8]. We reported the rising incidence of hepatitis C to the authorities in Belgium responsible for disease surveillance, in more detail than routine reporting. General practitioners were urged through widely read local medical journals to include hepatitis C testing for any MSM patient consulting for STI screening. The rising incidence was also picked up by the press. We also brought this growing problem to the attention of the Flemish organisation that is responsible for prevention of STIs (Sensoa). In collaboration with representatives of the gay scene, new prevention campaigns have been specifically

designed for HCV prevention in order to try to influence the target group, in particular in local risk settings and through specific Internet sites.

As reported previously, more research is needed to identify more clearly the circumstances of HCV transmission in HIV-positive MSM presenting with recurrent STIs [24]. Unprotected receptive anal intercourse, rough sexual techniques (receptive and insertive fisting) and nasal intake of recreational drugs have repeatedly been associated with increased risk of hepatitis C infection [7,17]. However, in our cohort a substantial number of infected patients do not report any of these practices (preliminary data of an ongoing case–control study). It remains unclear how far specific practices like those reported in certain hardcore clubs may also be incriminated in the spread of HCV, and to what extent the shared use of lubricants, sex toys (such as vibrators, clamps, chains and, dildos) or other more invasive devices (such as tubes for anal douching and urethral catheters) may also play a role in HCV transmission. As long as these questions are not fully answered it will be difficult to give evidence-based advice to some hard-to-reach subgroups of MSM (for example, fetishists and sadomasochists). We are now undertaking a case–control study looking at the incidence of HCV infection in our HIV-positive MSM population in relation to specific sexual practices. The reasons for the specific vulnerability of HIV-infected patients for HCV acquisition should also be clarified [7]. Further sociological and biomedical research should focus on the relative contributions of behavioural aspects (such as serosorting or traumatic practices) or of possible cellular or molecular mucosal modifications enhancing specifically STI and/or HCV acquisition in HIV-infected individuals [18].

Conclusion

Intensified and tailored surveillance is necessary to further document the rising incidence of HCV infection in MSM attending HIV/STI clinics in Europe. Identifying more accurately the risk factors for HCV acquisition and designing appropriate and highly contextualised prevention messages for risk groups are the two other major challenges healthcare providers are now facing. In the HIV-infected MSM population, HCV infection has become the most severe STI as its long-term impact may be devastating and its treatment options are far from optimal.

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