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Risk Factors for Sexual Transmission of Hepatitis C Virus Among Human Immunodeficiency Virus-Infected Men Who Have Sex With Men: A Case-Control Study

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Background. Since 2000, incidence of sexually acquired hepatitis C virus (HCV)-infection has increased among human immunodeficiency virus (HIV)-infected men who have sex with men (MSM). To date, few case-control and cohort studies evaluating HCV transmission risk factors were conducted in this population, and most of these studies were initially designed to study HIV-related risk behavior and characteristics.

Methods. From 2009 onwards, HIV-infected MSM with acute HCV infection and controls (HIV-monoinfected MSM) were prospectively included in the MOSAIC (MSM Observational Study of Acute Infection with hepatitis C) study at 5 large HIV outpatient clinics in the Netherlands. Written questionnaires were administered, covering socio-demographics, bloodborne risk factors for HCV infection, sexual behavior, and drug use. Clinical data were acquired through linkage with databases from the Dutch HIV Monitoring Foundation. For this study, determinants of HCV acquisition collected at the inclusion visit were analyzed using logistic regression.

Results. Two hundred thirteen HIV-infected MSM (82 MSM with acute HCV infection and 131 MSM without) were included with a median age of 45.7 years (interquartile range [IQR], 41.0–52.2). Receptive unprotected anal intercourse (adjusted odds ratio [aOR], 5.01; 95% confidence interval [CI], 1.63–15.4), sharing sex toys (aOR, 3.62; 95% CI, 1.04–12.5), unprotected fisting (aOR, 2.57; 95% CI, 1.02–6.44), injecting drugs (aOR, 15.62; 95% CI, 1.27–192.6), sharing straws when snorting drugs (aOR, 3.40; 95% CI, 1.39–8.32), lower CD4 cell count (aOR, 1.75 per cubic root; 95% CI, 1.19–2.58), and recent diagnosis of ulcerative sexually transmitted infection (aOR, 4.82; 95% CI, 1.60–14.53) had significant effects on HCV acquisition.

Conclusions. In this study, both sexual behavior and biological factors appear to independently increase the risk of HCV acquisition among HIV-infected MSM.

Keywords. hepatitis C virus; HIV-HCV coinfection; MSM; risk factors; sexual transmission.

Since 2000, outbreaks of sexually transmitted hepatitis C virus (HCV) have increasingly been reported among human immunodeficiency virus (HIV)-infected men who have sex with men (MSM) in Europe, Australia, Asia, and the United States [1–4]. Although some cases have been described to have acquired HCV through a

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sexual route in the absence of HIV [5], the HIV-uninfected MSM population remains largely unaffected by this epidemic [4, 6–9].

After the increase of HCV incidence among HIV-infected MSM, 3 case-control studies have been conducted to elucidate determinants for HCV infection [10–12]. However, the 2 studies that included participants prospectively [11, 12] comprised small numbers of cases with acute HCV infection: 34 and 22, respectively. Independent risk factors that were identified in the 3 case-control studies were as follows: receptive unprotected anal intercourse (UAI), sex while high on methamphetamines [12], rectal bleeding, frequent receptive fisting, snorting cocaine or amphetamines [11], and group sex participation [10, 11].

Determinants for acute HCV infection among HIV-infected MSM have also been investigated retrospectively, in large HIV cohort studies in the United States [13], Switzerland [14], the Netherlands [8], and Japan [15]. These cohort studies led to accurate estimates of HCV incidence. However, because the initial scope of these cohorts was to study HIV, data on HCV-specific risk factors were limited. Independent risk factors for HCV acquisition that were identified in these studies were as follows: younger age [8], positive hepatitis B surface antigen test, alcohol abuse, lower CD4 cell count [13], illicit drug use, being on social benefits [15], injecting drug use (IDU) [13, 15], receptive UAI with multiple partners, and recent syphilis infection [13, 14].

Various other studies that addressed potential risk factors for HCV infection were limited by their study design (cross-sectional studies including prevalent infections and case reports) [5, 7, 16–21]. Because the majority of the studied MSM had an unknown duration of HCV infection, the reported risk behavior and clinical parameters at the time of study may differ significantly from those at the time of HCV acquisition.

The MOSAIC (MSM Observational Study of Acute Infection with hepatitis C) cohort has been initiated to specifically study acute HCV infection among HIV-infected MSM. This cohort is one of the largest case-control studies conducted until now and therefore provides a unique opportunity to study biological and behavioral risk factors for sexual transmission of HCV.

METHODS

Study Population

The MOSAIC cohort is an open, ongoing, prospective, observational cohort, initiated to study determinants and sequelae of acute HCV infection among HIV-infected MSM [22]. The MOSAIC is a collaboration between the Public Health Service of Amsterdam, 5 large HIV outpatient clinics in the Netherlands (3 in Amsterdam, 1 in Rotterdam, and 1 in Utrecht), and the Dutch HIV Monitoring Foundation. Study subjects were HIV-infected MSM ≥18 years of age who (recently) had acquired an acute HCV infection. Acute HCV infection was defined as having an interval ≤6 months between the first positive HCV RNA test and the preceding negative HCV RNA or antibody test. To serve as controls, we aimed to include 2 HIV-infected MSM with no history of HCV, at the same hospital and in the period shortly after a case was identified. Inclusion started in 2009, and for the current study, we included all prospectively identified cases and controls who entered the study before February 2014.

Data Collection

Hepatitis C virus antibody testing was performed using either AxSYM HCV 3.0 (Abbott Laboratories, Abbott Park, IL), ARCHITECT Anti-HCV (Abbott Laboratories), or Liaison XL (DiaSorin, Saluggia, Italy). Hepatitis C virus RNA tests were performed using either the VERSANT HCV RNA Qualitative Assay (Siemens Medical Solutions Diagnostics, Tarrytown, NY), COBAS Ampliprep/COBAS TaqMan (CAP/CTM; Roche Diagnostics, Mannheim, Germany), or the Abbott m2000 sp/rt system (Abbott Laboratories). Participants were followed up every 6 months, and more often during treatment of HCV infection, at their HIV outpatient clinic. At inclusion and follow-up visits, participants completed a self-administered questionnaire regarding sociodemographics, bloodborne risk factors classically related to HCV (eg, blood transfusion, IDU), sexual behavior with steady and/or casual sex partner(s), sex-related variables (eg, number of casual sex partners, meeting location), drug use before/during sex, and quality of life. Clinical data, such as date of HIV diagnosis, CD4 cell count, HIV viral load, and use of combination antiretroviral therapy (cART), were acquired for each visit through linkage with databases from the Dutch HIV Monitoring Foundation. The HCV-negative status of controls was assured by confirming the absence of HCV antibodies at inclusion and follow-up visits. The study protocol was approved by the local ethics committee, and all participants provided written informed consent to participate in the study.

Statistical Analysis

Determinants of HCV infection that were collected using the baseline questionnaire administered at the inclusion visit were analyzed using logistic regression. In univariable analysis, Firth's penalized likelihood method [23] was used to obtain odds ratios (ORs) and 95% confidence intervals (CIs) when a cell in the analyzed table had zero frequency. Having unprotected sex only with a steady sex partner with a confirmed negative HCV status was not considered to be risk behavior for HCV. It has been suggested that HCV may also be transmitted from one receptive partner to another through (1) sharing contaminated sex toys or (2) contaminated gloves during fisting [11]. Fisting without gloves and fisting with gloves in the presence of group sex are therefore defined as "unprotected fisting" throughout this study. We assumed that use of sex toys without sharing, and fisting with gloves in the absence of group sex, did not elevate the risk of HCV acquisition. The number of casual sex partners was transformed as $^{2}\text{Log}(N + 1)$; HIV viral load was modeled as ^{10}Log-increment above 50 copies/mL (values ≤50

were set at zero); CD4 cell count was cubic root transformed, to make the relationship with the outcome (HCV acquisition) more linear.

To limit the number of risk factors included in multivariable logistic regression, we performed 2 separate analyses. The first analysis only included variables that [1] were expected to have a direct effect on HCV acquisition, ie, traditional risk factors and sexual behavior (see Table 2B and 2C), and [2] were significantly associated with acute HCV infection in univariable analysis ($P < .05$). The second multivariable analysis included variables that were significantly associated in the first multivariable analysis ($P < .05$), variables related to sexual behavior that were strongly associated ($P < .001$) with acute HCV in univariable analysis, and variables that might facilitate or enhance HCV transmission (ie, recent ulcerative sexually transmitted infection [STI], lower CD4 cell count). When investigating the influence of these facilitating circumstances, we checked for the presence of interactions. We assumed that each facilitating factor had an equal interaction effect on all variables related to sexual risk behavior. When significant ($P < .05$), the interaction term was added to the final model; otherwise, the facilitating factor was included in the model without an interaction term. All analyses were performed using Stata Intercooled 13.1 (StataCorp, College Station, TX).

RESULTS

General Population Characteristics

By February 1, 2014, 82 HIV-infected MSM with acute HCV infection (cases) and 131 HIV-infected controls had entered the MOSAIC study and completed the inclusion questionnaire. Characteristics of acute HCV infection (eg, HCV subtype, HCV RNA load at first positive visit, reported symptoms of acute infection) are shown in Table 1. The vast majority of participants were included in the Amsterdam region (95.3%), and most were of Western European ethnicity (79.3%). The median age at study entry was 45.7 years, which was lower among cases (43.1 years) than controls (49.4 years; $P < .001$) (Table 2A).

Risk Factors for Hepatitis C Virus: Univariable Analysis

Apart from IDU, which was reported by 10 of 82 cases (12.2%) versus 2 of 131 controls (1.5%), none of the traditional bloodborne risk factors were associated with acute HCV in univariable analysis (Table 2B). Sharing of needles was relatively uncommon among MSM who reported IDU (2 of 12; 16.7%).

Sexual risk behavior was higher among MSM with acute HCV compared with HCV-negative controls, and nearly all variables related to sexual risk behavior were associated with acute HCV infection. The following variables were strongly associated ($P < .001$) with acute HCV infection using univariable regression: receptive UAI, sharing sex toys, unprotected fisting, group sex participation, rimming, fingering, increasing number of casual sex partners, anal rinsing, rectal bleeding during or after having sex, and meeting casual sex partner(s) at sex parties (Table 2C and D).

Among 82 cases, 69 (84.1%) reported non-IDU in the 6 months preceding study entry versus 52.7% of the controls (69 of 131; OR, 2.60; 95% CI, 1.44–4.70; $P = .002$). Use of anally administered drugs was less common (reported by 18.3% of cases) than use of either orally administered drugs (OADs) or nasally administered drugs ([NADs] reported by 78.0% and 74.4% of cases, respectively). Oral administration of methamphetamines, ecstasy/3,4-methylenedioxymethamphetamine (MDMA), γ-hydroxybutyric acid (GHB)/γ-butyrolactone (GBL), and cannabis was associated with acute HCV infection. Nasal administration of amphetamines, cocaine, ketamine, and poppers was associated with HCV acquisition (all $P < .001$). When

Table 1. Characteristics of Acute HCV Infection Among 82 HIV-Infected Men Who Have Sex With Men[a]

Characteristic	Value
Year of HCV diagnosis	2010.5 (2010.0–2011.0)
No. of days between last negative and first positive HCV RNA sample[b]	148 (116–186)
No. of days between last negative and first positive anti-HCV sample	164 (118–218)
HCV load of first positive HCV RNA sample	4.5 $E10^5$ (1.2 $E10^4$–3.3 $E10^6$)[c]
Change in ALT concentration between last negative and first positive HCV sample[d]	99 (19–422)[e]
Peak ALT concentration between last negative HCV sample and ≤3 months after the first positive HCV sample	350 (164–653)[e]
HCV subtype; n (%)	
1a	52 (63.4)
1b	6 (7.3)
2b	10 (12.2)
4d	11 (13.4)
Unknown/not typable	3 (3.7)
Reported symptoms of acute infection; n (%)	
Joint pain	7 (8.5)
Jaundice	3 (3.7)
Fatigue	38 (46.3)
Muscle pain	14 (17.1)
Flu-like symptoms	23 (28.1)
Loss of appetite	17 (20.7)

Abbreviations: ALT, alanine aminotransferase; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MOSAIC, MSM Observational Study of Acute Infection with hepatitis C.

[a]MOSAIC study, the Netherlands, 2009–2014. Numbers are median (interquartile range) unless indicated otherwise.

[b]Data available for 52 of 82 cases.

[c]IU/mL.

[d]Data available for 58 of 82 cases.

[e]U/L.

Table 2. Determinants of Acute HCV Infection Among 213 HIV-Infected Men Who Have Sex With Men, of Whom 82 Had Acute Hepatitis C Infection

Characteristic	Subcategory	82 HIV+ MSM With Acute HCV N (%)	131 HIV+ MSM Without HCV N (%)	Odds Ratio (95% CI)	*P* Value
2A: SOCIODEMOGRAPHIC CHARACTERISTICS					
Age		43.1 (39.2–47.6)	49.4 (42.3–54.8)	0.94 (.38–.72) per 10-year increment	<.001
Ethnicity	Western European	65 (79.3)	104 (79.4)	1	.742
	Other	15 (20.7)	27 (20.6)	1.13 (.56–2.27)	
Living situation	Alone	32 (39.0)	57 (43.5)	1	.755
	With steady sex partner	38 (46.3)	54 (41.2)	1.25 (.69–2.28)	
	Other	12 (14.6)	20 (15.3)	1.07 (.46–2.47)	
Educational level	Middle and low	27 (32.9)	35 (26.7)	1	.277
	High	53 (64.6)	96 (73.3)	0.72 (.39–1.31)	
2B: TRADITIONAL RISK FACTORS FOR HCV [12M]					
Injecting drug use (IDU)		10 (12.2)	2 (1.5)	8.96 (1.91–42.01)	.005
Tattoo		6 (7.3)	9 (6.9)	1.07 (.37–3.12)	.901
Blood transfusion		0 (0.0)	2 (1.5)	0.31 (.01–6.62)	.456
Surgery		7 (8.5)	15 (11.5)	0.72 (.28–1.85)	.498
Endoscopy		9 (11.0)	15 (11.5)	0.95 (.40–2.29)	.915
2C: SEXUAL BEHAVIOR [6M]					
Insertive/receptive unprotected anal intercourse (iUAI/rUAI)	No UAI/only with HCV-negative steady sex partner	10 (12.2)	61 (46.6)	1	<.001
	Only iUAI with HCV-positive/ unknown sex partner(s)	3 (3.7)	15 (11.5)	1.22 (.30–4.99)	
	(Also) rUAI with HCV-positive/ unknown sex partner(s)	69 (84.1)	55 (42.0)	7.65 (3.59–16.31)	
Sharing of sex toys	No toys used/only shared toys with HCV-negative steady sex partner	55 (67.1)	126 (96.2)	1	<.001
	Toys shared	27 (32.9)	5 (3.8)	12.37 (4.53–33.81)	
Unprotected fisting	No fisting/gloves used and no group sex reported	42 (51.2)	113 (86.3)	1	<.001
	No gloves used/gloves used and group sex reported	40 (48.8)	18 (13.7)	5.98 (3.09–11.56)	
Group sex participation	No group sex	29 (35.4)	84 (64.1)	1	<.001
	With 2 sex partners (ie, only threesomes)	9 (11.0)	15 (11.5)	1.74 (.69–4.40)	
	With ≥3 sex partners	44 (53.7)	29 (22.1)	4.39 (2.34–8.26)	
Rimming	No rimming/only with HCV-negative steady sex partner	29 (35.4)	80 (61.1)	1	<.001
	(Also) with HCV-positive/ unknown sex partner(s)	53 (64.6)	51 (38.9)	2.87 (1.62–5.08)	

Table 2 continued.

Characteristic	Subcategory	82 HIV+ MSM With Acute HCV N (%)	131 HIV+ MSM Without HCV N (%)	Odds Ratio (95% CI)	*P* Value
Fingering	No fingering/only with HCV-negative steady sex partner	28 (34.1)	75 (57.3)	1	.001
	(Also) with HCV-positive/ unknown sex partner(s)	54 (65.9)	56 (42.7)	2.58 (1.46–4.58)	
2D: SEX-RELATED VARIABLES [6M]					
Having a steady sex partner		48 (58.5)	79 (60.3)	0.93 (.53–1.63)	.798
Age of steady sex partner		43 (40–49)	45 (36–50)	1.05 (.67–1.63) per 10-year increment	.831
Number of casual sex partners					
Continuous		11 (5–23)	5 (0–10)	1.38 (1.18–1.62) per doubling	<.001
Categorical	0	8 (9.8)	36 (27.5)	1	<.001
	1–9	25 (30.5)	47 (35.9)	2.39 (.97–5.93)	
	10–19	19 (23.2)	29 (22.1)	2.95 (1.13–7.70)	
	20–49	22 (26.8)	13 (9.9)	7.62 (2.72–21.29)	
	≥50	8 (9.8)	6 (4.6)	6.00 (1.62–22.16)	
Anal rinsing	No anal rinsing/only with HCV-negative steady sex partner	18 (22.0)	72 (55.0)	1	<.001
	Anal rinsing with HCV-positive/ unknown sex partner(s)	64 (78.0)	59 (45.0)	4.34 (2.32–8.11)	
Rectal bleeding during and/or after sex	No bleeding/only after sex with HCV-negative steady sex partner	46 (56.1)	117 (89.3)	1	<.001
	Bleeding after sex with HCV-positive/ unknown sex partner(s)	36 (43.9)	14 (10.7)	6.54 (3.23–13.24)	
Piercing(s) in genital region	No piercing(s)	73 (89.0)	125 (95.4)	1	.218
	Yes, self	3 (3.7)	2 (1.5)	2.57 (.42–15.73)	
	Yes, steady sex partner	6 (7.3)	4 (3.1)	2.57 (.70–9.40)	
Received money for sex		4 (4.9)	5 (3.8)	1.29 (.34–4.96)	.709
Meeting location of casual sex partner(s)					
Leather bar/leather party		20 (24.4)	21 (16.0)	1.69 (.85–3.36)	.134
Gay bar		22 (26.8)	27 (20.6)	1.41 (.74–2.70)	.295
Internet		51 (62.2)	55 (42.0)	2.27 (1.29–4.00)	.004
Public cruising area		5 (6.1)	16 (12.2)	0.47 (.16–1.33)	.153
Sex party		28 (34.2)	10 (7.6)	6.27 (2.85–13.83)	<.001
Gay sauna		20 (24.4)	34 (26.0)	0.92 (.49–1.74)	.799
Darkroom		21 (25.6)	32 (24.4)	1.07 (.56–2.01)	.846
Abroad		12 (14.6)	20 (15.3)	0.95 (.44–2.07)	.900
Other		8 (9.8)	10 (7.6)	1.31 (.49–3.46)	.589

Table 2 continued.

Characteristic	Subcategory	82 HIV+ MSM With Acute HCV N (%)	131 HIV+ MSM Without HCV N (%)	Odds Ratio (95% CI)	*P* Value
2E: DRUG USE BEFORE/DURING SEX [6M]					
Orally administered drugs (OADs)					
No OADs used		18 (22.0)	81 (61.8)	0.18 (.09-.33)	<.001
2C-B		0 (0.0)	1 (0.8)	0.52 (.02–13.10)	.696
Amphetamines		6 (7.3)	4 (3.1)	2.51 (.69–9.17)	.165
Cannabis		31 (37.8)	27 (20.6)	2.34 (1.27–4.33)	.007
Cocaine		4 (4.9)	2 (1.5)	3.31 (.59–18.48)	.173
Ecstasy/MDMA		57 (69.5)	32 (24.4)	7.05 (3.81–13.06)	<.001
GHB/GBL		39 (47.6)	22 (16.8)	4.49 (2.39–8.44)	<.001
Ketamine		1 (1.2)	0 (0.0)	4.84 (.19–12.2)	.336
Methamphetamines		9 (11.0)	0 (0.0)	33.99 (1.95–592.5)	.016
Poppers		4 (4.9)	3 (2.3)	2.19 (.48–10.04)	.314
Anally administered drugs (AADs)					
No AADs used		67 (81.7)	129 (98.5)	0.07 (.02–.31)	.001
Amphetamines		4 (4.9)	2 (1.5)	3.31 (.59–18.48)	.173
Cannabis		1 (1.2)	0 (0.0)	4.84 (.19–12.2)	.336
Cocaine		8 (9.8)	1 (0.8)	14.05 (1.72–114.6)	.014
GHB/GBL		1 (1.2)	1 (0.8)	1.60 (.10–26.02)	.739
Ketamine		7 (8.5)	2 (1.5)	6.02 (1.22–29.73)	.028
Methamphetamines		3 (3.7)	1 (0.8)	4.94 (.50–48.28)	.170
Poppers		1 (1.2)	0 (0.0)	4.84 (.19–12.2)	.336
Nasally administered drugs (NADs)					
No NADs used		21 (25.6)	83 (63.4)	0.20 (.11–.37)	<.001
Amphetamines		23 (28.0)	4 (3.1)	12.38 (4.10–37.40)	<.001
Cocaine		38 (46.3)	19 (14.5)	5.09 (2.65–9.77)	<.001
Ketamine		30 (36.6)	9 (6.9)	7.82 (3.47–17.62)	<.001
Methamphetamines		4 (4.9)	0 (0.0)	15.08 (.80–283.8)	.070
Mephedrone		2 (2.4)	2 (1.5)	1.61 (.22–11.68)	.636
Poppers		50 (61.0)	42 (32.1)	3.31 (1.86–5.89)	<.001
Methods of administering drug(s), combined	No drugs used	13 (15.9)	62 (47.3)	1	<.001
	Only OADs used	5 (6.1)	15 (11.5)	1.59 (.49–5.15)	
	NADs used, no straws shared	22 (26.8)	33 (25.2)	3.18 (1.42–7.11)	
	NADs used, straws shared	33 (40.2)	20 (15.3)	7.87 (3.48–17.80)	
	Injected drugs	9 (11.0)	1 (0.8)	42.92 (5.00–368.8)	

Table 2 continued.

Characteristic	Subcategory	82 HIV+ MSM With Acute HCV N (%)	131 HIV+ MSM Without HCV N (%)	Odds Ratio (95% CI)	*P* Value
2F: CLINICAL CHARACTERISTICS					
CD4 cell count at the HCV-negative visit preceding study entry (cells/μL)		500 (400–670)	590 (450–760)	1.41 (1.08–1.85) per cubic root lower	.012
Nadir CD4 cell count until the HCV-negative visit preceding study entry (cells/μL)		260 (170–350)	210 (110–310)	0.82 (.67–1.01) per cubic root lower	.057
No. of years between first HIV-positive test and study entry visit[a]		6.5 (3.2–9.7)	9.1 (4.0–15.4)	0.92 (.88–.97)	.001
HIV load at HCV-negative visit preceding study entry (copies/mL)		<50 (<50–12525)[b]	<50 (<50-<50)[b]	1.59 (1.18–2.12) per ^{10}Log increment	.002
Use of cART at HCV-negative visit preceding study entry[a]		68 (84.0)	111 (91.0)	0.52 (.22–1.22)	.133
STIs (self-reported) ^{6M}					
Syphilis		20 (24.4)	7 (5.3)	5.71 (2.29–14.24)	<.001
Chlamydia trachomatis		29 (35.4)	13 (9.9)	4.97 (2.39–10.31)	<.001
Rectal gonorrhea		19 (23.2)	5 (3.8)	7.60 (2.71–21.30)	<.001
Herpes genitalis		1 (1.2)	1 (0.8)	1.60 (.10–26.02)	.739
Hepatitis B virus		0 (0.0)	1 (0.8)	0.53 (.02–13.10)	.696
LGV		9 (11.0)	2 (1.5)	7.95 (1.67–37.80)	.009
Urethral gonorrhea		14 (17.1)	6 (4.6)	4.29 (1.58–11.67)	.004
Other (eg, genital warts, oral gonorrhea)		2 (2.4)	3 (2.3)	1.07 (.17–6.52)	.944
STIs (combined)	No STIs	34 (41.5)	109 (83.2)	1	<.001
	≥1 nonulcerative STI	22 (26.8)	13 (9.9)	5.43 (2.47–11.91)	
	≥1 ulcerative STI[c]	26 (31.7)	9 (6.9)	9.26 (3.96–21.67)	

Continuous variables are presented as median (interquartile range).

Abbreviations: 2C-B, 2,5-dimethoxy-4-bromophenethylamine hydrochloride; ^{6M}, up to 6 months preceding study entry; ^{12M}, up to 12 months preceding study entry; cART, combination antiretroviral therapy; CI, confidence interval; GBL, γ-butyrolactone; GHB, γ-hydroxybutyric acid; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HIV+ MSM, HIV-infected men who have sex with men; LGV, lymphogranuloma venereum; STI, sexually transmitted infection.

[a] Data missing for 1 case and 9 controls.

[b] Fifty of 75 (66.7%) cases and 99 of 112 (88.4%) controls had undetectable HIV viral load.

[c] Ulcerative STI: syphilis, herpes genitalis, LGV.

analyzed by means of administration, use of orally, anally, and nasally administered drugs were more frequently reported by cases than controls; ORs increased from 1.59 for the use of OADs only to 42.9 for injecting drugs (Table 2E). Sharing straws was reported by 51% of MSM who reported consumption of NADs, and it was significantly associated with HCV acquisition (OR for snorting drugs with vs without sharing straws: 2.48; 95% CI, 1.14–5.37).

Clinical variables associated with acute HCV were as follows: (1) lower CD4 cell count and higher HIV viral load at the last visit before inclusion (ie, for cases before acute HCV infection) and (2) shorter duration since HIV diagnosis (Table 2F). These associations remained statistically significant in a sensitivity analysis only including those on cART at the study entry visit (N = 179; data not shown). In addition, the association between HCV acquisition and CD4 cell count remained significant in a sensitivity analysis that included only cases with a known HCV RNA negative test date preceding study entry (N = 52; OR, 1.49 per cubic root lower; 95% CI, 1.08–2.05; $P = .015$). Syphilis, chlamydia, and rectal gonorrhea infection in the previous 6 months were strongly associated with acute HCV infection (all $P < .001$). Both nonulcerative and ulcerative STIs were more often reported by MSM with acute HCV than MSM with no history of HCV (Table 2F).

Risk Factors for Hepatitis C Virus Acquisition: Multivariable Analysis

In the first multivariable analysis that included variables that may directly cause transmission of acute HCV, receptive UAI (adjusted OR [aOR], 4.92; 95% CI, 2.00–12.10; $P = .001$), sharing sex toys (aOR, 6.08; 95% CI, 1.96–18.87; $P = .002$), unprotected fisting (aOR, 2.60; 95% CI, 1.11–6.10; $P = .028$), IDU (aOR, 11.26; 95% CI, 1.21–105.2; $P = .034$), and sharing straws when snorting drugs (aOR, 3.79; 95% CI, 1.71–8.42; $P = .001$) had significant effects on HCV acquisition. Group sex participation, rimming, and fingering had no significant effects on HCV acquisition (Figure 1A); these variables were therefore omitted in the second multivariable analysis.

In the second multivariable analysis that included a broader range of variables, none of the studied interactions were significant, and they were therefore omitted in the presented model. In this model, receptive UAI (aOR, 5.01; 95% CI, 1.63–15.43; $P = .005$), sharing sex toys (aOR, 3.62; 95% CI, 1.04–12.52; $P = .042$), unprotected fisting (aOR, 2.57; 95% CI, 1.02–6.44; $P = .044$), IDU (aOR, 15.62; 95% CI, 1.27–192.6; $P = .032$), sharing straws when snorting drugs (aOR, 3.40; 95% CI, 1.39–8.32; $P = .007$), lower CD4 cell count (aOR, 1.75 per cubic root lower; 95% CI, 1.19–2.58; $P = .004$), and recent ulcerative STI (aOR, 4.82; 95% CI, 1.60–14.53; $P = .005$) had significant effects on HCV acquisition. The number of casual sex partners had no significant effect on HCV acquisition; nor did anal rinsing, rectal bleeding, and sex parties as meeting location for casual sex partners (Figure 1B).

In an exploratory post hoc analysis, we calculated a risk score for each MSM, ranging from 0 to 6, depending on the number of the following sexual behavior acts in the 6 months preceding study entry: receptive UAI, sharing toys, unprotected fisting, group sex participation, rimming, fingering. In multivariable analysis, men with a risk score of 4 had an aOR of 8.63 (95% CI, 1.49–50.0), those with risk score of 5 had an aOR of 10.3 (95% CI, 1.54–68.4), and 12 men with a risk score of 6 were excluded from the analysis because all 12 were cases, leading to a zero cell count. Men with risk scores of 1, 2, and 3 of these sex acts had aORs of 2.61 (95% CI, .52–13.1), 2.16 (95% CI, .38–12.4), and 2.40 (95% CI, .48–12.0), respectively, compared with MSM with a zero risk score. In this analysis, the aOR for the variables that were added in the second multivariable analysis were comparable (data not shown).

DISCUSSION

We conducted a comprehensive study on risk factors for transmission of HCV among HIV-infected MSM showing that receptive UAI, sharing sex toys, unprotected fisting, IDU, sharing straws when snorting drugs, lower CD4 cell count, and recent ulcerative STI have independent effects on HCV acquisition among HIV-infected MSM. Most of these variables were not independently associated with acute HCV in previously conducted case-control studies [10–12], probably due to a lack of statistical power, or because these studies did not incorporate data on all topics mentioned. Other transmission routes that previously have been suggested (eg, rectal bleeding [11]) were measured, but they had no significant effect on HCV acquisition in our multivariable analysis.

MSM with acute HCV infection were younger than controls, concurrent with other recent studies [8, 24, 25]. In addition, cases had shorter duration of (known) HIV infection, but they had lower CD4 cell counts preceding HCV acquisition than HCV-negative controls. Although the absolute difference in median CD4 cell count was 90 cells/μL (ie, 500 for cases vs 590 for controls), the effect remained significant in multivariable analysis (also when the CD4 cell count obtained from the penultimate visit was analyzed). An effect of lower CD4 cell count on HCV acquisition has been suggested before, but studies addressing this topic are scarce. Witt et al [13] reported significantly higher HCV incidence rates among HIV-infected MSM with lower CD4 cell counts (modeled per 100 cells/μL for those with a range of 0–500). In contrast, in the Swiss HIV Cohort Study [14] and the Amsterdam Cohort Study among MSM [8], effects of CD4 cell count on HCV acquisition were marginal and not significant. The lower CD4 cell count that we observed may be a consequence of STI other than HCV [26] and thereby an indirect marker for earlier increased sexual risk behavior. The significant effect of a reduced CD4 cell count may partly explain why

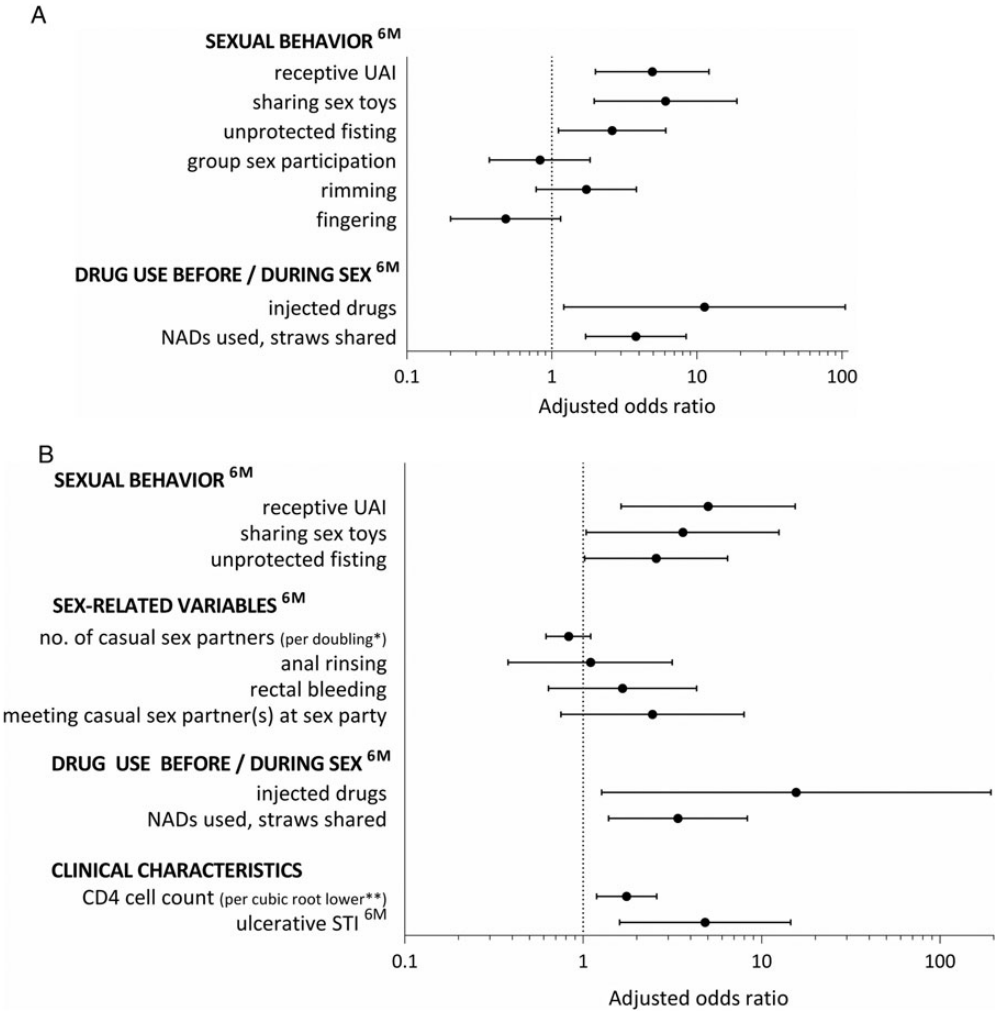

Figure 1. A, Cleveland dot plot showing results of a multivariable model including variables that potentially have direct effects on acquisition of acute hepatitis C virus (HCV); model 1 of 2. B, Cleveland dot plot showing (1) results of a multivariable model including variables that potentially have direct effects on acquisition of acute HCV and (2) variables that potentially facilitate transmission of acute HCV, model 2 of 2. *, modeled as ^{2}Log(N + 1); **, at the HCV-negative visit preceding study entry, cells/μL. ^{6M}, up to 6 months preceding study entry; NADs, nasally administered drugs; UAI, unprotected anal intercourse; ulcerative STI, any of the following sexually transmitted infections: syphilis, herpes genitalis, lymphogranuloma venereum. Data were collected among 213 human immunodeficiency virus (HIV)-infected men who have sex with men (MSM), 82 of whom had acute HCV infection. All participated in the MOSAIC (MSM Observational Study of Acute Infection with hepatitis C) study, the Netherlands, 2009–2014.

sexual transmission of HCV infection seems to be rare among HIV-negative MSM [1, 5]. Alternatively, lower sexual risk behavior among HIV-negative MSM might explain the absence of both HIV and HCV in this group. Another reason there may be increased HCV infection among HIV-infected MSM compared with HIV-negative MSM could be due to serosorting (ie, establishing HIV concordance in advance to practicing UAI) [27].

The associations of HCV acquisition with group sex participation, the number of casual sex partners, and meeting location of casual sex partners lost significance when corrected for sexual behavior in multivariable analysis. Hence, the sexual behavior itself (eg, having receptive UAI or not) appeared to outweigh the number of casual sex partners (either simultaneous or consecutive) in contributing to risk of acute HCV infection. In addition, the risk score analysis also showed that men who participated in 4 or more different risky sex acts in the previous 6 months were much more likely to have acquired HCV than men with less than 4 sex acts. This finding emphasizes that there are differences in the degree of sexual risk taking among MSM, and it indicates that practicing multiple risky sexual techniques may substantially increase the risk of HCV acquisition.

The majority of HCV infections in our study was of genotype 1 and 4, in line with earlier reports [7, 8, 10, 12, 14, 28]. We report a relatively high proportion of subtype 2b infections

(12.2%); this subtype is likely to have been introduced more recently in the MSM population in the Netherlands [8, 29].

In contrast to recent findings in the United Kingdom [30], we did not observe a high prevalence of so-called "chem-sex" or "slamming" (ie, injection of methamphetamines or mephedrone in combination with high-risk sexual practices). Injecting drug use and, more specifically, sharing needles was relatively uncommon in our study. Still, IDU remains a major risk factor for transmission of HCV. Sharing straws was reported by more than half of the participants that had recently consumed NADs; it had a significant effect on HCV acquisition in the multivariable analyses. Although sharing of contaminated straws could potentially increase HCV transmission [31], a systematic review regarding this topic concluded that current studies failed to show clear associations of non-IDU behavior with HCV infection [32]. Hence, whether or not sharing straws is a direct or indirect route of HCV transmission remains to be elucidated. Administration of NADs, or drug use in general, could be a marker for risky behavior that we did not measure, eg, longer sex episodes or having more rough sex. This may lead to dehydration of mucosal surfaces, which in turn may increase chances of permucosal transmission of HCV due to microtrauma or rectal bleeding [10]. A reason for not finding an association of HCV acquisition with rectal bleeding in our multivariable analysis might be underreporting, because not all bleeding is visible during or after sex [11].

This study has some limitations. The sample size still limits the number of parameters that could be estimated in multivariable analysis (including interaction terms). Diagnosis of recent STI was self-reported, and use (or sharing) of lubricant was not assessed; the latter might also facilitate HCV transmission. Various HIV-related characteristics were studied, but the precise duration of HIV infection could only be estimated for a minority of the population because for most participants, no data on HIV-negative test results were available. Because different risk behaviors might be correlated, it could be difficult to determine which is the more important one leading to HCV acquisition. However, correlation is unlikely to be a significant factor in our study, because it would have led to less significant effects of different sexual behaviors in multivariable analysis. As characteristics of local epidemics may differ (eg, the difference in the practice of chem-sex reported in this study compared with reports from the United Kingdom [30]), and the majority of participants in our study were from Amsterdam and the Netherlands, our results may not be widely generalizable to other areas.

CONCLUSIONS

This study showed significant effects of both biological and behavioral risk factors on HCV acquisition among MSM. In the ongoing HCV epidemic in which HIV-infected MSM with high-risk sexual behavior were probably infected first, MSM with lower risk profiles may become increasingly affected by acute HCV [7, 33]. Frequent testing of MSM at highest risk for (re-)infection may lead to earlier diagnosis and treatment initiation, which in turn could also limit ongoing transmission in the MSM population. In addition, tailored education and behavioral interventions are therefore needed to avoid ongoing transmission of HCV in the MSM population. Future longitudinal studies should preferably focus on temporal changes in risk behavior among HIV-infected MSM, to evaluate possible risk reduction strategies for HCV (re-)infection.

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References

1. Bradshaw D, Matthews G, Danta M. Sexually transmitted hepatitis C infection: the new epidemic in MSM? Curr Opin Infect Dis **2013**; 26:66–72.
2. van de Laar TJ, Matthews GV, Prins M, Danta M. Acute hepatitis C in HIV-infected men who have sex with men: an emerging sexually transmitted infection. AIDS **2010**; 24:1799–812.
3. van der Helm JJ, Prins M, del Amo J, et al. The hepatitis C epidemic among HIV-positive MSM: incidence estimates from 1990 to 2007. AIDS **2011**; 25:1083–91.
4. Yaphe S, Bozinoff N, Kyle R, et al. Incidence of acute hepatitis C virus infection among men who have sex with men with and without HIV infection: a systematic review. Sex Transm Infect **2012**; 88:558–64.
5. van de Laar TJ, Paxton WA, Zorgdrager F, et al. Sexual transmission of hepatitis C virus in human immunodeficiency virus-negative men who have sex with men: a series of case reports. Sex Transm Dis **2011**; 38:102–4.
6. Schmidt AJ, Falcato L, Zahno B, et al. Prevalence of hepatitis C in a Swiss sample of men who have sex with men: whom to screen for HCV infection? BMC Public Health **2014**; 14:3.

7. Urbanus AT, van de Laar TJ, Geskus R, et al. Trends in hepatitis C virus infections among MSM attending a sexually transmitted infection clinic; 1995–2010. AIDS **2014**; 28:781–90.
8. Vanhommerig JW, Stolte IG, Lambers FA, et al. Stabilizing incidence of hepatitis C virus infection among men who have sex with men in Amsterdam. J Acquir Immune Defic Syndr **2014**; 66:e111–5.
9. Jin F, Prestage GP, Matthews G, et al. Prevalence, incidence and risk factors for hepatitis C in homosexual men: data from two cohorts of HIV-negative and HIV-positive men in Sydney, Australia. Sex Transm Infect **2010**; 86:25–8.
10. Danta M, Brown D, Bhagani S, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. AIDS **2007**; 21:983–91.
11. Schmidt AJ, Rockstroh JK, Vogel M, et al. Trouble with bleeding: risk factors for acute hepatitis C among HIV-positive gay men from Germany–a case-control study. PLoS One **2011**; 6:e17781.
12. Centers for Disease Control and Prevention (CDC). Sexual transmission of hepatitis C virus among HIV-infected men who have sex with men–New York City, 2005–2010. MMWR Morb Mortal Wkly Rep **2011**; 60:945–50.
13. Witt MD, Seaberg EC, Darilay A, et al. Incident hepatitis C virus infection in men who have sex with men: a prospective cohort analysis, 1984–2011. Clin Infect Dis **2013**; 57:77–84.
14. Wandeler G, Gsponer T, Bregenzer A, et al. Hepatitis C virus infections in the Swiss HIV Cohort Study: a rapidly evolving epidemic. Clin Infect Dis **2012**; 55:1408–16.
15. Nishijima T, Shimbo T, Komatsu H, et al. Incidence and risk factors for incident hepatitis C infection among men who have sex with men with HIV-1 infection in a large urban HIV clinic in Tokyo. J Acquir Immune Defic Syndr **2014**; 65:213–7.
16. Sanchez C, Plaza Z, Vispo E, et al. Scaling up epidemics of acute hepatitis C and syphilis in HIV-infected men who have sex with men in Spain. Liver Int **2013**; 33:1357–62.
17. Urbanus AT, van de Laar TJ, Stolte IG, et al. Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic. AIDS **2009**; 23:F1–7.
18. Matthews GV, Pham ST, Hellard M, et al. Patterns and characteristics of hepatitis C transmission clusters among HIV-positive and HIV-negative individuals in the Australian trial in acute hepatitis C. Clin Infect Dis **2011**; 52:803–11.
19. Gambotti L, Batisse D, Colin-de-Verdiere N, et al. Acute hepatitis C infection in HIV positive men who have sex with men in Paris, France, 2001–2004. Euro Surveill **2005**; 10:115–7.
20. Serpaggi J, Chaix ML, Batisse D, et al. Sexually transmitted acute infection with a clustered genotype 4 hepatitis C virus in HIV-1-infected men and inefficacy of early antiviral therapy. AIDS **2006**; 20:233–40.
21. Montoya-Ferrer A, Fierer DS, Alvarez-Alvarez B, et al. Acute hepatitis C outbreak among HIV-infected men, Madrid, Spain. Emerg Infect Dis **2011**; 17:1560–2.
22. Lambers FA, Brinkman K, Schinkel J, et al. Treatment of acute hepatitis C virus infection in HIV-infected MSM: the effect of treatment duration. AIDS **2011**; 25:1333–6.
23. Firth D. Bias reduction of maximum likelihood estimates. Biometrika **1993**; 80:27–38.
24. Garg S, Taylor LE, Grasso C, Mayer KH. Prevalent and incident hepatitis C virus infection among HIV-infected men who have sex with men engaged in primary care in a Boston community health center. Clin Infect Dis **2013**; 56:1480–7.
25. Rauch A, Rickenbach M, Weber R, et al. Unsafe sex and increased incidence of hepatitis C virus infection among HIV-infected men who have sex with men: the Swiss HIV Cohort Study. Clin Infect Dis **2005**; 41:395–402.
26. Jarzebowski W, Caumes E, Dupin N, et al. Effect of early syphilis infection on plasma viral load and CD4 cell count in human immunodeficiency virus-infected men: results from the FHDH-ANRS CO4 cohort. Arch Intern Med **2012**; 172:1237–43.
27. Owen G. An 'elephant in the room'? Stigma and hepatitis C transmission among HIV-positive 'serosorting' gay men. Cult Health Sex **2008**; 10:601–10.
28. Martin TC, Martin NK, Hickman M, et al. HCV reinfection incidence and treatment outcome among HIV-positive MSM. AIDS **2013**; 27:2551–7.
29. Markov PV, van de Laar TJ, Thomas XV, et al. Colonial history and contemporary transmission shape the genetic diversity of hepatitis C virus genotype 2 in Amsterdam. J Virol **2012**; 86:7677–87.
30. Kirby T, Thornber-Dunwell M. High-risk drug practices tighten grip on London gay scene. Lancet **2013**; 381:101–2.
31. Aaron S, McMahon JM, Milano D, et al. Intranasal transmission of hepatitis C virus: virological and clinical evidence. Clin Infect Dis **2008**; 47:931–4.
32. Scheinmann R, Hagan H, Lelutiu-Weinberger C, et al. Non-injection drug use and Hepatitis C Virus: a systematic review. Drug Alcohol Depend **2007**; 89:1–12.
33. McFaul K, Maghlaoui A, Nzuruba M, et al. Acute hepatitis C infection in HIV-negative men who have sex with men. J Viral Hepat **2015**; 22:535–8.