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
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, 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 $^{10}\log$-increment above 50 copies/mL (values ≤50 copies/mL were set to 0 for further analysis).
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; oth-
erwise, the facilitating factor was included in the model without an 
interaction term. All analyses were performed using Stata Inter-
cooled 13.1 (StataCorp, College Station, TX).

RESULTS

General Population Characteristics

By February 1, 2014, 82 HIV-infected MSM with acute HCV 
inefction (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 in-
fecrion) 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 blood-
borne risk factors were associated with acute HCV in univar-
iable 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 vari-
ables 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 regres-
sion: 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 metham-
phetamines, ecstasy/3,4-methylenedioxymethamphetamine 
(MDMA), γ-hydroxybutyric acid (GHB)/γ-butyrolactone (GBL), 
and cannabis was associated with acute HCV infection. Nasal 
administration of amphetamine, cocaine, ketamine, and poppers 
was associated with HCV acquisition (all \(P < .001\).

### Table 1. Characteristics of Acute HCV Infection Among 82 HIV-

Infected Men Who Have Sex With Men*:

| 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 \[^c\] | \(4.5 \times 10^6\) (1.2 \(\times 10^6\–3.3 \times 10^6\)) |
| Change in ALT concentration between last negative and first positive HCV sample \[^d\] | 99 (19–422) |
| Peak ALT concentration between last negative HCV sample and ≤3 months after the first positive HCV sample | 350 (164–653) |
| 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 (%); \[^e\] | |
| 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.

\[^*\]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** |                                      |                                  |                               |                     |         |
| 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**             |                                      |                                  |                               |                     |         |
| 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) |         |
| 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 ^SM     | Having a steady sex partner                                                  | 48 (68.5)                        | 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                                                                 | 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 (9.9)                          | 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 (1.34–4.96)    | .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 (1.6–1.33)     | .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    |
| 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** |                              |                                  |                                |                     |              |
| Oral 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                |              |
| Methamphetamine            | 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                |              |
| Anal y 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                |              |
| Methamphetamine            | 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)                       | 5.08 (2.65–9.77)               | <.001               |              |
| Ketamine                   | 30 (36.6)                     | 9 (6.9)                         | 7.82 (3.47–17.62)              | <.001               |              |
| Methamphetamine            | 4 (4.9)                       | 0 (0.0)                         | 15.08 (8.0–283.8)              | .070                |              |
| Mephedrone                 | 2 (2.4)                       | 2 (1.5)                         | 1.61 (1.22–11.68)              | .636                |              |
| Poppers                    | 50 (61.0)                     | 42 (32.1)                       | 3.31 (1.86–5.69)               | <.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 |
|--------------------------------------------------------------------------------------------|-----------------------------------|--------------------------------|---------------------|---------|
| **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**                          | 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)                  | <50 (<50–<50)                 | 1.59 (1.18–2.12) per 10Log increment | .002    |
| **Use of cART at HCV-negative visit preceding study entry**                              | 68 (84.0)                       | 111 (91.0)                    | 0.52 (.22–1.22)     | .133    |
| **STIs (self-reported)**                                                                 |                                   |                               |                     |         |
| 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 nonulcerative STI                                                                       | 34 (41.5)                        | 109 (83.2)                    | 1                   | <.001   |
| ≥1 ulcerative STI                                                                           | 22 (26.8)                        | 13 (9.9)                      | 5.43 (2.47–11.91)   |        |
| ≥1 ulcerative STI                                                                            | 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.

Data missing for 1 case and 9 controls.

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

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
The 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 methamphetamine 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 percutaneous 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 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 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.

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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