Unsafe Sex and Increased Incidence of Hepatitis C Virus Infection among HIV-Infected Men Who Have Sex with Men: The Swiss HIV Cohort Study

Andri Rauch,[1] Martin Rickenbach,[2] Rainer Weber,[3] Bernard Hirschel,[4] Philip E. Tarr,[5] Heiner C. Bucher,[6] Pietro Vernazza,[7] Enos Bernasconi,[8] Annelies S. Zinkernagel,[3] John Evison,[1] and Hansjakob Furrer,[1] and the Swiss HIV Cohort Study[a]

[1]Division of Infectious Diseases, University Hospital Berne, [2]Data Center Swiss HIV Cohort Study, Lausanne, [3]Division of Infectious Diseases, University Hospital Zurich, [4]Division of Infectious Diseases, University Hospital Geneva, [5]Division of Infectious Diseases, University Hospital Lausanne, [6]Basel Institute for Clinical Epidemiology, University Hospital Basel, [7]Division of Infectious Diseases, Kantonsspital St. Gallen, and [8]Division of Infectious Diseases, Ospedale Civico Lugano, Switzerland

Background. Data on the incidence of hepatitis C virus (HCV) infection among human immunodeficiency virus (HIV)–infected persons are sparse. It is controversial whether and how frequently HCV is transmitted by unprotected sexual intercourse.

Methods. We assessed the HCV seroprevalence and incidence of HCV infection in the Swiss HIV Cohort Study between 1988 and 2004. We investigated the association of HCV seroconversion with mode of HIV acquisition, sex, injection drug use (IDU), and constancy of condom use. Data on condom use or unsafe sexual behavior were prospectively collected between 2000 and 2004.

Results. The overall seroprevalence of HCV infection was 33% among a total of 7899 eligible participants and 90% among persons reporting IDU. We observed 104 HCV seroconversions among 3327 participants during a total follow-up time of 16,305 person-years, corresponding to an incidence of 0.64 cases per 100 person-years. The incidence among participants with a history of IDU was 7.4 cases per 100 person-years, compared with 0.23 cases per 100 person-years in patients without such a history ($P < .001$). In men who had sex with men (MSM) without a history of IDU who reported unsafe sex, the incidence was 0.7 cases per 100 person-years, compared with 0.2 cases per 100 person-years in those not reporting unsafe sex ($P = .02$), corresponding to an incidence rate ratio of 3.5 (95% confidence interval, 1.2–10.0). The hazard of acquiring HCV infection was elevated among younger participants who were MSM.

Conclusions. HCV infection incidence in the Swiss HIV Cohort Study was mainly associated with IDU. In HIV-infected MSM, HCV infection was associated with unsafe sex.

Chronic infection with hepatitis C virus (HCV) is a major cause of morbidity and mortality in HIV-infected persons in the era of potent antiretroviral therapy [1]. Transmission routes of HCV infection are injection drug use (IDU) with needle sharing, occupational exposure in health care workers, contaminated blood products, transplants, use of medical and paramedical devices, and vertical transmission. Whether and how frequently HCV is transmitted by unprotected sexual contacts remains controversial [2].

In Switzerland, the incidence of acute hepatitis C in the years 1992–2002 varied from 0 to 4 cases per 100,000 person-years, depending on the observed age group, with a maximum incidence among those aged 20–30 years [3]. However, official incidences generally underestimate true infection rates in the population, because they depend on the completeness of case reporting, and because many asymptomatic cases of HCV infection are not diagnosed.

Information on HCV prevalence in HIV-infected persons is available in different settings. However, little is known about the incidence of HCV infection in this patient group, mainly because of a paucity of prospective cohorts with long term follow-up data. In the

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[a] Members of the Swiss HIV Cohort Study are listed at the end of the text.

Reprints or correspondence: Dr. Hansjakob Furrer, Div. of Infectious Diseases, University Hospital, Inselspital PKT2B, CH-3010 Bern (hansjakob.furrer@insel.ch).

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Women's Interagency HIV Study, a low incidence of 0.27 infections per 100 person-years was found, and most of these infections could be attributed to IDU [4]. A high incidence of HCV infection among injection drug users was found irrespective of HIV serostatus in different cohorts with incidence rates of 8–41 cases per 100 person-years [5–9].

Data from serodiscordant, mainly heterosexual couples indicate that HCV is rarely transmitted by sexual intercourse, even in patients coinfected with HIV [10–13]. Nevertheless, it has been suggested that HIV infection may be a cofactor for sexual transmission of HCV [14]. Ulcerous infections of the genital tract might facilitate HCV infection. However, only sparse data are available on the incidence of HCV infection among persons with high-risk sexual behavior. Although prevalence rates of up to 10% in men who have sex with men (MSM) have been observed, they could be attributed mainly to concurrent IDU [15]. In an Italian sexually transmitted disease clinic, incidence rates were found to be 1.3 and 0.9 cases per 100 person-years [16] for MSM and heterosexual persons, respectively. HIV-infected persons had a trend towards a higher incidence of HCV infection. Intriguing recent reports suggest increasing HCV infection rates in HIV-infected MSM who do not consistently use condoms [17].

In the Swiss HIV Cohort Study (SHCS), seroprevalence of HCV is repeatedly measured in seronegative persons, and information regarding IDU and condom use is collected every 6 months from all participants. For these reasons, we were able to study the incidence of HCV infection in relation to sexual behavior and drug use.

PATIENTS AND METHODS

The SHCS (available at http://www.shcs.ch) is a prospective cohort study with ongoing enrolment of adult HIV-infected patients [18]. Patients are followed-up in 1 of 7 study centers. Information is collected according to standardized criteria on structured forms at enrolment and at follow-up visits at 6-month intervals. At these occasions, plasma from blood samples is stored at −70°C for every patient. Written informed consent is mandatory for inclusion in the study, and the study has been approved by all local ethical committees. All authors had full access to all of the data in the Swiss HIV Cohort Study and had final responsibility for the decision to submit this article for publication.

HCV and syphilis serological testing. Routine serological testing for HCV infection was introduced in 1998. In 1999, serological testing was performed retrospectively on stored samples for all patients actively followed-up in the SHCS at that time [19]. In HCV-seronegative SHCS participants, HCV serological testing is performed every 2 years with a third-generation ELISA. Positive results are confirmed by immunoblot. Additional testing for HCV infection is at the discretion of the treating physicians.

With regard to classical sexually transmissible diseases, only the results of serological testing for syphilis (*Treponema pallidum* hemagglutination assay, TPHA) are recorded at study inclusion in approximately two-thirds of the patients.

Sexual behavior and IDU. Information regarding IDU or the participation in drug-substitution programs is collected at entry to the cohort and at every follow-up visit. Patients who reported to have a history of IDU at entry or reported IDU or participation in a drug-substitution program at least once during follow-up were classified as having a history of IDU.

The standardized questions regarding sexual behavior and consistency of condom use were changed several times during the past 16 years. The most recent change took place in April 2000 [20, 21]. Since then, participants reporting anal or vaginal sexual intercourse have been asked whether they used condoms always, sometimes, or never in either a stable partnership or with occasional partners. Participants who reported that they did not always use condoms were classified as having a history of unsafe sex. Participants who chose not to answer the question were classified as practising safer sex. A sensitivity analysis was performed classifying those who chose not to answer as practising unsafe sex.

Patients in the different analyses. The number of patients used for the analyses in the study differed with regard to available data. For prevalence data, all 7899 patients who were tested for hepatitis C at entry into the study were included. For incidence calculation, all 3327 patients who tested initially seronegative for hepatitis C and underwent at least 1 serological test during follow-up were included. For incidence calculation that included data on condom use, all 3166 patients who were seronegative in April 2000 and had at least 1 serological follow-up test thereafter were included.

Statistical analysis. We used the SHCS database, updated in June 2004, for analysis. For the subgroup analysis about condom use, we used only data after 1 April 2000. Prevalence of HCV infection was defined as the proportion of participants with a positive serological test result out of those for whom a test was performed.

Incidences were determined as seroconversions per 100 person-years. The number of HCV seroconversions was divided by the total time between first and last HCV test in participants with negative HCV test results at time of enrolment. Individual follow-up time was censored at the time of the first positive HCV serological test result or the time of the last follow-up that included HCV serotesting.

For definitions of 95% CIs, a Poisson distribution of the seroconversions was assumed. Differences between subgroups were analyzed using Poisson regression. Survival curves were established with the Kaplan-Meier method, and survival was

compared using the log-rank test. The Cox proportional hazards model was used to test independent effects of explanatory variables. Trend statistics among ordered groups were performed using the nonparametric test described by Cuzick [22]. The statistical package Stata SE, version 8.2 (Stata) was used for analysis.

RESULTS

Prevalence of HCV infection. Table 1 depicts the characteristics of and HCV seroprevalence among the 7899 participants for whom HCV serotesting was performed. The prevalence of HCV infection among persons with a presumed HIV transmission caused by IDU was >90%. There were 357 participants who were classified as having a history of IDU but who were not classified as having a presumed HIV transmission route of IDU. The respective prevalence rates are shown in the lower part of table 1.

Association of serological test results positive for syphillis and HCV prevalence. In patients with a presumed sexual mode of HIV transmission and no history of IDU, the prevalence of serological test results positive for syphilis was evaluated in both HCV-positive and HCV-negative individuals. In the heterosexual transmission group, 5 (4.3%) of 113 HCV-seropositive individuals and 112 (6.5%) of 1732 HCV-seronegative individuals had positive TPHA results ($P = .4$). In the MSM transmission group, the respective numbers were 13 (4.7%) of 277 HCV-seropositive participants and 34 (2.3%) of 1499 HCV-seronegative participants ($P = .02$).

Incidence of HCV infection. In 1830 (34.8%) of the 5157 participants who were initially seronegative for HCV, no serological follow-up data were available, and they were therefore excluded from incidence calculations. The excluded patients differed epidemiologically from those with follow-up data. HIV transmission route for the excluded patients was less likely to

Table 1. Characteristics of and seroprevalence of hepatitis C virus (HCV) infection among 7899 Swiss HIV Cohort Study (SHCS) participants with ⩾1 serological test result for HCV.

	SHCS participants with ⩾1 serological test result for HCV	
Variable	All	With results positive for HCV[a]
No. (%) of patients	7899 (100)	2638 (33)
Age, median years (IQR)		
Overall	35 (30–42)	
Male patients	37 (32–43)	
Female patients	33 (28–38)	
Sex		
Male	5451 (69)	1694 (31)
Female	2448 (31)	944 (39)
Presumed HIV transmission route or group		
Heterosexual sex	2811 (36)	392 (14)
MSM	2550 (32)	108 (4)
IDU	2244 (28)	2080 (93)
Blood products	85 (1)	34 (40)
Other, unknown	209 (3)	24 (11)
History of IDU		
Overall	2601 (33)	2329 (90)
With a presumed HIV transmission route other than IDU, by route or group		
Heterosexual sex	274	217 (79)
MSM	67	23 (34)
Blood products	3	3 (100)
Other or unknown	13	6 (46)

NOTE. Data are no. (%) of patients, unless otherwise specified. IQR, interquartile range; MSM, men who have sex with men.

[a] Data are no. (%) of patients in the specified subgroup with results positive for HCV, unless otherwise specified.

be sex between MSM (41% vs. 49%) and more likely to be heterosexual sex (52% vs. 43%); correspondingly, excluded participants were more likely than others to be female (31% vs. 23%), but there was no difference in the age distribution.

In the remaining 3327 participants with follow-up data, we observed a total of 104 cases of HCV seroconversion during a total observation time of 16,305 person-years. The median observation time was 4.4 years (interquartile range, 2.9–6.2 years). This resulted in an overall incidence of 0.64 cases per 100 person-years (95% CI, 0.52–0.77 cases per 100 person-years).

The incidences of HCV in different subgroups are shown in table 2 and figure 1*A*. A history of IDU was associated with a ~30-fold increase in risk of acquiring HCV infection.

HCV seroconversion and ongoing IDU. Among the participants with a history of IDU, the incidences differed according to the reported mode of drug use during the follow-up period. The incidences in the respective groups were 5.5 cases per 100 person-years (95% CI, 3.6–7.8 cases per 100 person-years) in 549 participants who denied IDU or participation in a drug-substitution program during follow-up, 5.4 cases per 100 person-years (95% CI, 2.4–12.5 cases per 100 person-years) in 93 participants in a drug-substitution program with no IDU, 13.2 cases per 100 person-years (95% CI, 8.1–20.5 cases per 100 person-years) in 151 participants in a drug-substitution program with concurrent IDU, and 9.7 cases per 100 person-years (95% CI, 5.3–16.2 cases per 100 person-years) in 145 individuals who did not participate in a drug-substitution program but reported IDU during follow-up. In a multivariate Poisson regression analysis involving patients with a history of IDU, incidence rate ratios were 2.0 (95% CI, 1.2–3.3) for patients with continuing IDU ($P = .01$) and 1.2 (95% CI, 0.7– 2.1) for patients with participation in a drug-substitution program ($P = .5$) during follow-up.

HCV seroconversion and sexual behavior. A total of 3166 participants who were HCV seronegative at the first visit after 1 April 2000 contributed to the analysis of the association of HCV incidence with unsafe sex. The presumed HIV transmission route or group was heterosexual sex in 1383 participants (44%), MSM in 1571 (50%), IDU in 74 (2%), and other or unknown in 138 (4%). IDU was reported by 36 (2.6%) of the heterosexual patients and 29 (1.8%) of the MSM; these participants were excluded from the analysis of the association of HCV incidence with unsafe sex. In the remaining heterosexual transmission group, 752 (56%) were women. Unsafe sex was reported by 401 (30%) of the heterosexual transmission group (25% by men and 34% by women) and by 414 (27%) in the MSM transmission group. In the youngest quartile of age (younger than 32.5 years) of MSM participants, unsafe sex was reported by 36%. This proportion was significantly smaller in the older age groups: 28%, 24%, and 20% in the second, third, and fourth quartile of age respectively ($P < .001$ for trend).

We observed an apparently higher incidence of HCV infection in recent years among patients without a history of IDU (table 2). However, this finding should be interpreted cau-

Table 2. Incidence rates of hepatitis C virus (HCV) infection among 3327 Swiss HIV Cohort Study participants with initial serological test results negative for HCV.

Patient characteristic	No. of patients with HCV seroconversion	Incidence per 100 person-years (95% CI)	Incidence rate ratio (95% CI)[a]	*P*
Sex				
Female	32	0.79 (0.54–1.1)	1.33 (0.89–1.24)	.2
Male	72	0.59 (0.46–0.74)		
Heterosexual HIV acquisition in patients without IDU, by sex				
Female	6	0.17 (0.06–0.37)	0.96 (0.29–3.13)	.9
Male	5	0.18 (0.06–0.42)		
History of IDU				
Yes	69	7.4 (5.7–9.3)	32.3 (21.5–48.5)	<.001
No	35	0.23 (0.15–0.31)		
Observation period for patients without IDU				
Before April 2000	12	0.15 (0.08–0.27)		
After April 2000	23	0.28 (0.18–0.42)		
MSM without IDU[b]				
Unsafe sex	8	0.70 (0.30–1.4)	3.45 (1.21–10.04)	.02
Safe sex	6	0.20 (0.07–0.43)		

NOTE. IDU, injection drug use; MSM, men who have sex with men.

[a] Incidence rate ratios are calculated using Poisson regression analysis

[b] With follow-up after April 2000.

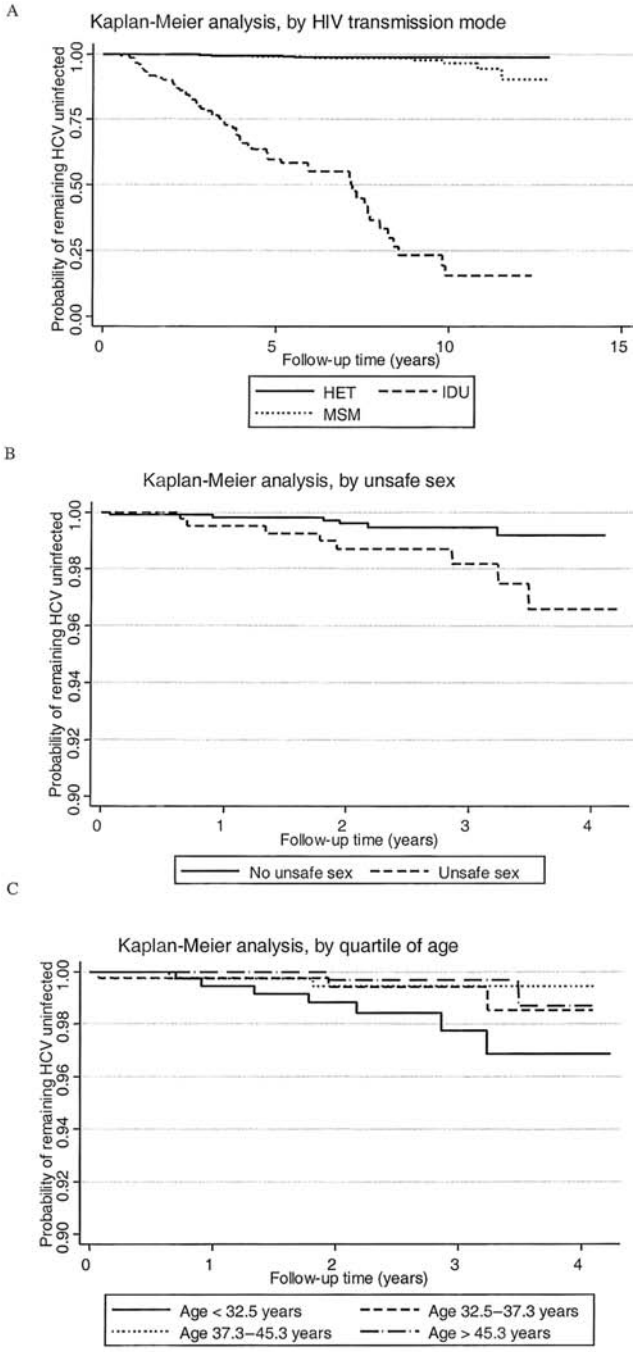

Figure 1. Kaplan-Meier estimates of probability of remaining uninfected with hepatitis C virus (HCV) in patients with initial serological test results negative for HCV according to presumed HIV transmission route *(A),* according to reported unsafe sex *(B)* among men who have sex with men (MSM), and in the MSM group according to quartiles of age *(C).* In panel *A,* all patients with a presumed sexual HIV transmission route but with a history of injection drug use (IDU) were excluded from analysis. In the log rank test, there was a highly significant difference between the IDU group and the sexual transmission route groups ($P < .0001$, by the log-rank test), whereas no difference was found between the heterosexual transmission route (HET) group and the MSM group ($P = .6$, by the log rank test). In panel *B,* all patients with a history of IDU were excluded from analysis. Participants reporting unsafe sex had a greater probability of acquiring HCV infection ($P = .01$, by the log rank test). In panel *C,* all patients with a history of IDU were excluded from analysis. There was a significant trend towards a higher risk of acquiring HCV infection in younger participants ($P = .02$, by the log rank test).

tiously, because serological analyses were partly performed retrospectively before April 2000.

In participants with presumed HIV transmission by MSM contacts, the incidence of HCV infection was significantly higher for those who reported unsafe sex than for those who did not (table 2). The association of unsafe sex and HCV acquisition was further analyzed using Cox proportional hazards models in participants without a history of IDU and presumed sexual transmission of HIV (table 3). There was a statistically significant association between reporting of unsafe sex and the hazard of HCV seroconversion. This association was significant in the participants with HIV transmission by MSM (figure 1*B*), but it did not reach statistical significance in participants with heterosexual transmission.

In addition, younger MSM participants had a higher risk of HCV seroconversion. This association was statistically significant in the univariate survival analysis (figure 1*C*) and remained a trend in the Cox proportional hazards model (table 3).

Given the association of HCV prevalence and syphilis prevalence in MSM participants, we introduced the results of serological testing for syphilis at baseline into the Cox proportional hazards model of HCV infection. Because information about serological testing for syphilis at baseline was not available for one-third of the patients, this model had less power than did the former model. There was a significant association of a positive TPHA result at baseline and the risk of HCV seroconversion, with an adjusted hazard ratio of 4.6 (95% CI, 1.2–17.4; $P = .03$); however, in this model, the parameter of unsafe sex was not significantly associated with the risk of HCV seroconversion (adjusted hazard ratio, 2.0; 95% CI, 0.6–6.9; $P = .3$).

Sensitivity analysis. A sensitivity analysis classifying those who chose not to answer the question about condom use as practising unsafe sex was performed. All of the significant associations in table 2, as well as the log rank statistics of figures 1*A*, 1*B*, and 1*C*, remained. However, for the association in the multivariable Cox proportional hazards model of MSM (table 3), the adjusted hazard ratio for unsafe sex was 2.8 (95% CI, 0.97–8.2; $P = .056$), whereas the estimate for quartiles of age remained in the same range.

DISCUSSION

Because chronic hepatitis C is a major cause of morbidity and mortality in persons with HIV-HCV coinfection in the era of potent antiretroviral therapy [1], every measure should be taken to prevent HCV infection. Our analysis shows continuing HCV infection in a nationwide cohort of adult persons with HIV infection in Switzerland. HCV incidence is highest in persons with a history of IDU, with incidence rates of 5–13 cases per 100 person-years. HCV infections occur also in persons without reported IDU, although at an incidence rate 30 times lower. Intriguingly, HCV infection is associated with inconsistent condom use in MSM in our cohort.

Despite well-functioning drug-substitution and harm-reduction programs in Switzerland [23–25], IDU remains the major risk factor for acquiring HCV infection in our cohort. This is reflected by the high prevalence of HCV infection (>90%) found in HIV-infected persons with a history of IDU

Table 3. Cox proportional hazards models for acquiring hepatitis C virus (HCV) infection for Swiss HIV Cohort Study participants with follow-up after April 2000 and without a history of injection drug use (IDU).

Subpopulation, parameter	Adjusted hazard ratio (95% CI)	*P*
All participants without history of IDU		
Female	0.4 (0.1–1.6)	.18
Unsafe sex	3.4 (1.5–7.8)	.004
Heterosexual HIV transmission route	0.9 (0.11–7.0)	.9
MSM	0.9 (0.11–6.7)	.9
Participants with heterosexual HIV transmission mode		
Female	0.6 (0.13–2.6)	.5
Unsafe sex	3.0 (0.74–12.2)	.1
Age per quartile increase	1.7 (0.8–3.5)	.2
Participants with MSM HIV transmission mode		
Unsafe sex	3.0 (1.03–8.8)	.04
Age per quartile increase	0.6 (0.37–1.06)	.08

NOTE. The hazard ratio is adjusted for all variables in the table. MSM, men who have sex with men.

[a] Statistically significant.

entering the SHCS. Despite regular care in specialized centers, the incidence of HCV infection among participants with continuing IDU remains in the range of 10 cases per 100 person-years. More emphasis should therefore be given to informing patients about this risk, allowing injection drug users safe injection procedures, and establishing opiate-substitution programs.

Among persons without a history of IDU, the incidence of HCV infection is much lower. The transmission route of these infections is unclear. Unsafe medical procedures are unlikely to have a major impact in established health care settings, but paramedical and nonmedical interventions, such as acupuncture or tattooing [26], remain a possible route of transmission. The possibility of HCV transmission by sharing materials used for intranasal cocaine use remains controversial [27–29].

HCV infections in serodiscordant couples are rarely observed, at least not in heterosexual couples [10, 12, 30]. Many experts therefore conclude that sexual transmission of HCV is of little importance. Nevertheless, concurrent genital ulcers caused by genital herpes simplex or syphilis might facilitate transmission of HCV if condoms are not consistently used [31]. In some studies, HCV prevalence was associated with increased numbers of sexual partners and intercourses, especially among MSM [32–34]; others, however, could not find such an association [35]. These contradictory results can be explained by differences in study design, because most study were cross-sectional analyses. In addition, immunodeficiency associated with concurrent HIV infection may influence the threshold of HCV infectivity.

Although our findings were based on a small number of seroconversions, we found a statistically significant association between reporting unsafe sex and HCV infection among MSM in recent years. We conclude that inconsistent condom use bears a small but significant risk for HCV infection in unprotected male homosexual contacts. Of note, there are recent reports of small epidemics of HCV infection in the gay community [17]. We observed a significant trend towards an increased risk of HCV seroconversion in younger MSM. If HCV is sexually transmissible, this finding is in concordance with a recent report about a lower adherence to safer sex in younger participants in the SHCS [21] and with the higher proportion of younger MSM participants in this analysis reporting unsafe sex. The association between serological test results positive for syphilis and the incidence of HCV infection in the MSM population further points towards possible sexual transmission of HCV infection.

With regard to heterosexual relationships without consistent condom use, our data do not show a statistically significant increased risk of HCV infection; however, the point estimate of the hazard ratio for unsafe sex was 3.0. This clearly does not allow one to exclude such a risk.

To our knowledge, this is the first report of an association of unsafe sex with an increased incidence of HCV infection in HIV-infected MSM that was determined on the basis of prospective longitudinal cohort data that included regular HCV testing and reports about condom use and IDU. Limitations of our analyses are that we cannot totally exclude confounding, because we did not ask for data on other risks for acquisition of HCV infection. One might hypothesize that sexual risk behavior might be a surrogate for other risk behavior, such as tattooing or intranasal drug use. In addition, data about sexual behavior and IDU are based on self-reporting. Self-reporting of behaviors considered to be irresponsible may be less consistent than other methods of reporting. This could favor underreporting of IDU in MSM. On the other hand, if HCV really is sexually transmissible, underreporting of unsafe sex would weaken the association described above. Another potential limitation is that we cannot rule out the possibility of seroreversion of the results of serological testing for HCV from negative to positive in patients previously infected with HCV who had lost anti-HCV antibodies because of severe HIV-induced immunodeficiency [36, 37].

In conclusion, data of the large, prospective SHCS indicate that unsafe sexual behavior among MSM is associated with new acquisition of HCV infection and that HCV seroconversion continues to occur among IDU, even though needle exchange programs are available in Switzerland. Thus, physicians caring for HIV-infected persons need to emphasize the prevention of HCV infection among their patients with continuing IDU and motivate MSM to practice safe sex because of the additional risk of transmitting and acquiring HCV infection.

THE SWISS HIV COHORT STUDY

M. Battegay, E. Bernasconi, J. Böni, H. Bucher, Ph. Bürgisser, S. Cattacin, M. Cavassini, R. Dubs, M. Egger, L. Elzi, P. Erb, K. Fantelli, M. Fischer, M. Flepp, A. Fontana, P. Francioli (President of the SHCS, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland), H. Furrer (Chairman of the Clinical and Laboratory Committee), M. Gorgievski, H. Günthard, B. Hirschel, L. Kaiser, C. Kind, Th. Klimkait, B. Ledergerber, U. Lauper, M. Opravil, F. Paccaud, G. Pantaleo, L. Perrin, J.-C. Piffaretti, M. Rickenbach (Head of the Data Center), C. Rudin (Chairman of the Mother and Child Substudy), P. Schmid, J. Schüpbach, R. Speck, A. Telenti, A. Trkola, P. Vernazza (Chairman of the Scientific Board), R. Weber, and S. Yerly.

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References

1. Sulkowski MS, Thomas DL. Hepatitis C in the HIV-infected person. Ann Intern Med **2003**; 138:197–207.
2. Yen T, Keeffe EB, Ahmed A. The epidemiology of hepatitis C virus infection. J Clin Gastroenterol **2003**; 36:47–53.
3. Bundesamt für Gesundheit. Infektionskrankheiten, schweiz 2001. **2003**. Available at: http://www.bag.admin.ch/infreporting/gs01/d/index.htm. Accessed 14 February 2005.
4. Augenbraun M, Goedert JJ, Thomas D, et al. Incident hepatitis C virus in women with human immunodeficiency virus infection. Clin Infect Dis **2003**; 37:1357–64.
5. van Beek I, Dwyer R, Dore GJ, Luo K, Kaldor JM. Infection with HIV and hepatitis C virus among injecting drug users in a prevention setting: retrospective cohort study. BMJ **1998**; 317:433–7.
6. Des J, Diaz T, Perlis T, et al. Variability in the incidence of human immunodeficiency virus, hepatitis B virus, and hepatitis C virus infection among young injecting drug users in New York City. Am J Epidemiol **2003**; 157:467–71.
7. Crofts N, Jolley D, Kaldor J, van Beek I, Wodak A. Epidemiology of hepatitis C virus infection among injecting drug users in Australia. J Epidemiol Community Health **1997**; 51:692–7.
8. Crofts N, Aitken CK. Incidence of bloodborne virus infection and risk behaviors in a cohort of injecting drug users in Victoria, 1990–1995. Med J Aust **1997**; 167:17–20.
9. Judd A, Hickman M, Jones S, et al. Incidence of hepatitis C virus and HIV among new injecting drug users in London: prospective cohort study. BMJ **2005**; 330:24–5.
10. Marincovich B, Castilla J, del Romero J, et al. Absence of hepatitis C virus transmission in a prospective cohort of heterosexual serodiscordant couples. Sex Transm Infect **2003**; 79:160–2.
11. Zylberberg H, Thiers V, Lagorce D, et al. Epidemiological and virological analysis of couples infected with hepatitis C virus. Gut **1999**; 45:112–6.
12. Vandelli C, Renzo F, Romano L, et al. Lack of evidence of sexual transmission of hepatitis C among monogamous couples: results of a 10-year prospective follow-up study. Am J Gastroenterol **2004**; 99: 855–9.
13. Neumayr G, Propst A, Schwaighofer H, Judmaier G, Vogel W. Lack of evidence for the heterosexual transmission of hepatitis C. QJM **1999**; 92:505–8.
14. Eyster ME, Alter HJ, Aledort LM, Quan S, Hatzakis A, Goedert JJ. Heterosexual cotransmission of hepatitis C virus (HCV) and human immunodeficiency virus (HIV). Ann Intern Med **1991**; 115:764–8.
15. Bodsworth NJ, Cunningham P, Kaldor J, Donovan B. Hepatitis C virus infection in a large cohort of homosexually active men: independent associations with HIV-1 infection and injecting drug use but not sexual behavior. Genitourin Med **1996**; 72:118–22.
16. Giuliani M, Caprilli F, Gentili G, et al. Incidence and determinants of hepatitis C virus infection among individuals at risk of sexually transmitted diseases attending a human immunodeficiency virus type 1 testing program. Sex Transm Dis **1997**; 24:533–7.
17. Browne R, Asboe D, Gilleece Y, et al. Increased numbers of acute hepatitis C infections in HIV-positive homosexual men: is sexual transmission feeding the increase? Sex Transm Infect **2004**; 80:326–7.
18. Sudre P, Rickenbach M, Taffé P, et al. Clinical epidemiology and research on HIV infection in Switzerland: the Swiss HIV Cohort Study 1988–2000. Schweiz Med Wochenschr **2000**; 130:1493–500.
19. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. Lancet **2000**; 356:1800–5.
20. Wolf K, Young J, Rickenbach M, et al. Prevalence of unsafe sexual behavior among HIV-infected individuals: the Swiss HIV Cohort Study. J Acquir Immune Defic Syndr **2003**; 33:494–9.
21. Glass TR, Young J, Vernazza PL, et al. Is unsafe sexual behavior increasing among HIV-infected individuals? AIDS **2004**; 18:1707–14.
22. Cuzick J. A Wilcoxon-type test for trend. Stat Med **1985**; 4:87–90.
23. Haemmig RB. Harm reduction in Bern: from outreach to heroin maintenance. Bull N Y Acad Med **1995**; 72:371–9.
24. Gschwend P, Rehm J, Blattler R, et al. Dosage regimes in the prescription of heroin and other narcotics to chronic opioid addicts in Switzerland: Swiss National Cohort Study. Eur Addict Res **2004**; 10:41–8.
25. Klingemann HK. Drug treatment in Switzerland: harm reduction, decentralization, and community response. Addiction **1996**; 91:723–36.
26. Delage G, Infante-Rivard C, Chiavetta JA, Willems B, Pi D, Fast M. Risk factors for acquisition of hepatitis C virus infection in blood donors: results of a case-control study. Gastroenterology **1999**; 116: 893–9.
27. Tortu S, McMahon JM, Pouget ER, Hamid R. Sharing of noninjection drug-use implements as a risk factor for hepatitis C. Subst Use Misuse **2004**; 39:211–24.
28. McMahon JM, Simm M, Milano D, Clatts M. Detection of hepatitis C virus in the nasal secretions of an intranasal drug-user. Ann Clin Microbiol Antimicrob **2004**; 3:6.
29. Wasley A, Alter MJ. Epidemiology of hepatitis C: geographic differences and temporal trends. Semin Liver Dis **2000**; 20:1–16.
30. Bresters D, Mauser-Bunschoten EP, Reesink HW, et al. Sexual transmission of hepatitis C virus. Lancet **1993**; 342:210–1.
31. Marx MA, Murugavel KG, Tarwater PM, et al. Association of hepatitis C virus infection with sexual exposure in southern India. Clin Infect Dis **2003**; 37:514–20.
32. Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med **1999**; 341:556–62.
33. Gasparini V, Chiaramonte M, Moschen ME, et al. Hepatitis C virus infection in homosexual men: a seroepidemiological study in gay clubs in north-east Italy. Eur J Epidemiol **1991**; 7:665–9.
34. Osmond DH, Charlebois E, Sheppard HW, et al. Comparison of risk factors for hepatitis C and hepatitis B virus infection in homosexual men. J Infect Dis **1993**; 167:66–71.
35. Weinstock HS, Bolan G, Reingold AL, Polish LB. Hepatitis C virus infection among patients attending a clinic for sexually transmitted diseases. JAMA **1993**; 269:392–4.
36. Chamot E, Hirschel B, Wintsch J, et al. Loss of antibodies against hepatitis C virus in HIV-seropositive intravenous drug users. AIDS **1990**; 4:1275–7.
37. John M, Flexman J, French MA. Hepatitis C virus-associated hepatitis following treatment of HIV-infected patients with HIV protease inhibitors: an immune restoration disease? AIDS **1998**; 12:2289–93.