

## SHORT REPORT

## Absence of hepatitis C virus transmission in a prospective cohort of heterosexual serodiscordant couples

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**Objective:** To analyse hepatitis C virus (HCV) transmission in a cohort of heterosexual couples who are discordant both for HIV and for HCV.

**Methods:** We followed an open cohort of 171 people, 152 women and 19 men, who were not initially infected by either HIV or HCV, and whose steady heterosexual partner presented antibodies to both viruses (index case). Other risk exposures were excluded. Every 6 months clinical, epidemiological, and risk behaviour information was collected, and antibodies to both viruses were determined.

**Results:** During 529 person years of follow up more than 40 000 vaginal or anal penetrations were recorded. 74 partners (43.3%) had vaginal and/or anal intercourse without condoms with the index case; another 15.8%, who always used condoms, declared breaking or slipping episodes during intercourse; and another 22.2% had unprotected orogenital exposures. During the follow up, over 5800 unprotected vaginal and anal contacts with the index case were estimated, as well as more than 25 000 unprotected orogenital contacts. 31 women became pregnant (two were index cases), and seroconversion to HIV occurred for one woman (1.7 per 10 000 unprotected contacts; 95% CI, 0 to 9.5), but there was no seroconversion to HCV (95% CI, 0–6.3 per 10 000 unprotected contacts).

**Conclusion:** These results are consistent with a low or null transmissibility of HCV in heterosexual relations, even when the index case is HIV co-infected.

Sexual transmission of hepatitis C virus (HCV) is still debated.<sup>1</sup> Various studies have provided evidence of possible cases of transmission by this route.<sup>2–5</sup> HCV RNA has been detected in the semen of one third of viraemic men, suggesting that the semen could be infectious.<sup>6</sup> Nevertheless, some reports suggest that sexual transmission can be very low or null when any parenteral exposures are taken into account.<sup>7–11</sup> It has been underlined that HIV-1 co-infection could increase the risk of sexual transmission of HCV,<sup>12–14</sup> although other studies did not confirm this finding.<sup>8</sup>

The majority of investigations on this subject show important limitations in establishing the time association between exposure and infection, and in excluding other risk exposures.<sup>1</sup> Prospective cohorts of steady sexual couples would be the most adequate design in order to overcome such limitations, but such studies are scarce.<sup>3,4</sup> The ones that exist calculated incidence rates according to the number of person years of follow up, without taking into consideration the fact that the number of sexual risk exposures can vary greatly with time.

The present study aims at estimating HCV seroconversion rates in a cohort of people with initial negative results to HCV and HIV tests, and whose sole known exposure has been

sexual intercourse with a steady partner who presents positive antibodies to both viruses.

**METHODS**

In a HIV counselling and testing clinic we followed an open cohort of people who were initially HIV seronegative (considered as “partners”), and whose steady heterosexual partner had had a confirmed HIV-1 infection diagnosis (considered as “index cases”). Both members of each couple were followed in the same clinic with regular half yearly examinations carried out separately. All these examinations were made by two practitioners, who collected, through a structured questionnaire, epidemiological and sexual behaviour information, as well as data concerning other parenteral or sexual risk exposures. It was explicitly asked about the practice of each type of sexual intercourse (vaginal, anal, and oral) during the period since the last visit. For each of these types of practices, the numbers of protected (with condom) and unprotected contacts were estimated, based on the monthly or weekly mean number of times it had been practised. We also asked if breaking or slipping of condom had occurred during penetration.

In all visits, clinical and analytical information about the index case was collected, and determination of antibodies to HIV-1/2 and to HCV was performed for the member of the couple who initially had not been infected. For HIV-1/2 the enzyme immunoassay (EIA) was used, and western blot was carried out for confirmation. Anti-HCV antibodies were assayed by second and third generation EIA, and immunoblot was used for confirmation.

Of the 253 couples with the index case presenting positive antibodies to HCV at the first visit, the prospective cohort study only included the 171 couples who were initially serodiscordant for HCV and who went through two or more medical check ups. The follow up period was from January 1991 to December 2001. People who showed any parenteral or sexual risk exposure different from sex with the index case were excluded from analysis. The possibility was ruled out that the last determination might coincide with a window period, by checking results of tests realised in later examinations, until July 2002. Incidence rates and their 95% confidence intervals (CI) were calculated using the number of person years and the number of times for unprotected intercourse during follow up period as denominators.

**RESULTS**

A total of 171 people from the cohort, 19 men and 152 women who initially were seronegative both for HIV and for HCV, and whose index case was seropositive for both viruses, were included in the analysis. Their mean age was 29.3 years. All index cases showed previous behaviour of injecting drug use. The median time of the relationship before beginning of follow up was 3.0 years, but 53 couples (31.0%) had started the relationship in the previous 12 months.

During the study period, 529 person years of follow up were counted and more than 40 000 vaginal or anal coitus. Of the

**Table 1** Description of the cohort of people with an HIV and HCV co-infected regular heterosexual partner

	No	%
All couples	171	100.0
Sex of the initially uninfected partner		
Men	19	11.1
Women	152	88.9
Age at the beginning of follow up, mean (range)	29.3 (18–49)	
Number of years of relationship with partner previous to beginning of follow up, median (range)	3.0 (0–27.4)	
People with sexual risk exposures	139	81.3
Vaginal or anal penetrations without condom*	74	43.3
Breaking or slipping of condom during vaginal or anal sex*	47	27.5
Unprotected orogenital sex*	119	69.6
People who had no unprotected sexual contact	32	18.7
Events that occurred during follow up (529 person years)		
Women who became pregnant	31	18.1
Seroconversions to HIV	1	0.6
Seroconversions to HCV	0	0
AIDS stage in index case	24	14.0
CD4+ cell count lower than $200 \times 10^6/l$	28	16.4

\*Some people had more than one type of sexual exposure.

**Table 2** Estimated number of risk exposures with HIV and HCV co-infected regular heterosexual partner, among the 171 people of the cohort, without there occurring any case of seroconversion to HCV

	Sex		Years of relationship with partner			Total
	Men	Women	<1	1–5	>5	
Unprotected vaginal or anal intercourse	420	5472	746	1623	3523	5892
Breaking or slipping of condom during vaginal or anal sex	6	90	28	38	30	96
Unprotected orogenital contacts	1243	24854	2873	9755	13469	26097

171 partners included in the study, only 74 (43.3%) had vaginal ( $n = 73$ ) and/or anal ( $n = 8$ ) intercourse without condoms with the index case during follow up; 47 partners (27.5%) declared breaking or slipping of condom during intercourse; and 119 (69.6%) had unprotected orogenital exposures. When taking into account all these results, a total of 101 partners (59.1%) from the cohort presented vaginal or anal risk exposures, owing to the absence of use of condom or to its slipping or breaking during coitus; 38 other partners (22.2%) were only exposed to risk through unprotected orogenital contacts; and the remaining 32 partners (18.7%) did not have unprotected exposure during follow up. Among the index cases, 24 had an AIDS defining illness and 28 showed a CD4+ cell count lower than  $200 \times 10^6/l$  (table 1).

During follow up a total of more than 5800 vaginal and anal coitus without condom with the infected partner was estimated, as well as more than 25 000 unprotected orogenital contacts (table 2). Also, 96 episodes of condom breakage or slippage happened during anal or vaginal penetration.

A total of 31 women became pregnant, of whom two were index cases. Seroconversion to HIV-1 occurred for one woman who had had unprotected vaginal sex with her index case. This man had an AIDS diagnosis, a CD4+ count of  $130 \text{ cells} \times 10^6/l$ , and a viral load of  $35\,410 \text{ copies per } 10^3/l$ . This single seroconversion implies an incidence rate of 1.9 per 1000 person years, and of 1.7 per 10 000 vaginal or anal intercourses without condom (95% CI, 0 to 9.5 per 10 000). There was no seroconversion to HCV, which enables us to obtain a 95% CI for the observed null seroconversion rate of 0–6.3 per 10 000 vaginal or anal intercourses without condoms, and of 0–1.4 per 10 000 unprotected orogenital practices.

Cross section analysis of the 253 couples with an HCV positive index case gave seven partners (2.8%, 95% CI 1.2 to 5.9) with positive antibodies to HCV at enrolment. Nevertheless,

for these seven cases non-sexual HCV transmission could not be totally excluded, since all of them reported previous accidental exposures to blood, injecting drug use or untested transfusions.

## DISCUSSION

After following a cohort of people whose steady heterosexual partner presented positive antibodies to HIV-1 and to HCV, and taking into account a high number of unprotected sexual exposures, we did not observe any seroconversion to HCV. In the mean time, for 31 of these couples pregnancy occurred and in one case we observed seroconversion to HIV-1. Among the partners of an HCV positive heterosexual index case, the seroprevalence of HCV antibodies at enrolment was 2.8%; nevertheless, all seropositive partners had had other situations with possible non-sexual risk exposure, and HCV infection before the start of the current relationship cannot be ruled out.

These results do not enable us to exclude the possibility of HCV transmission through sexual intercourse in heterosexual relationships, but do suggest that this transmission mechanism is inefficient,<sup>2–4 8–14</sup> even when the index case is HIV-1 co-infected. They are also consistent with other studies that consider HCV as less efficient for sexual transmission than HIV.<sup>3 10 11</sup>

The main limitation of this study is that a higher number of observations would have been necessary in order to obtain more precise estimations, given that risk is so low. Sixty nine per cent of couples were included in the study after more than 12 months had passed since the beginning of the relationship; if HCV transmission risk were much higher during these first months then this study could be underestimating the transmission rate.

### Key messages

- In a prospective cohort study of serodiscordant couples for hepatitis C virus, after more than 25 000 unprotected orogenital contact, and 5800 episodes of vaginal and anal intercourse without a condom, no seroconversion occurred
- These results are consistent with a very low or null transmissibility of hepatitis C virus in heterosexual relationships
- In order to quantify more exactly the possible sexual risk of hepatitis C virus transmission, we have to take into account other risk exposures; and large prospective studies can be useful

As opposed to other studies,<sup>7-16</sup> we explicitly assessed that the people included in the cohort study were HCV and HIV negative at beginning of follow up and, moreover, we left out people with previous parenteral risk exposures, such as those with tattooing, piercing, untested transfusions, and other percutaneous exposures to contaminated blood. Some authors have underlined that the sharing of glass syringes may have played an important part in HCV transmission between spouses.<sup>9</sup>

The risk of HCV transmission through unprotected orogenital contacts has been scarcely studied. Our study provides some information about this subject, as we observed that after more than 25 000 contacts of this type not a single case of transmission occurred.

Our experience reveals the interest in studying transmission risk according to the number of risk exposures and not only according to the number of person years of follow up, since the number of sexual risk exposures per unit of time may vary greatly. Among HCV serodiscordant couples, especially if they are also HIV discordant, use of condoms may well be extended as a way of avoiding possible risk of transmission to the partner, and this may affect comparability of results from different studies.

In order to reach more conclusive results about the HCV transmission risk through heterosexual practices, large prospective studies can be useful, which take into account parenteral risk exposures during follow up, and which evaluate the type and frequency of sexual exposures with the index case.

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### CONTRIBUTORS

JR, BM, and JC had the original idea; JR and SG attended all patients and filled in the questionnaires; CR performed the serological determinations; BM, VH, and MR extracted the data and created the database; BM and JC performed the statistical analyses; MR and BM performed the literature search; BM and JC wrote the first draft and all the authors contributed to the final version of the paper; JR, SG, CR, and JC are guarantors.

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