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 behaviour

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Objective: To determine the prevalence and risk factors for hepatitis C virus (HCV) infection in a cohort of homosexually active men, with particular reference to assessing sexual transmission.
Design: Prevalence based on cross-sectional testing for HCV (c100 protein) antibody in a cohort using sera stored between 1984 and 1989, and assessment of risk factors using a case-control analysis based on questionnaire data from HCV positive and negative subjects.
Subjects/setting: 1038 homosexually active men who were participating in a prospective study established to identify risk factors for AIDS. They had been recruited through private and public primary care and sexually transmissible disease (STD) services in central Sydney.
Main outcome measures: Prevalence of HCV antibody and its association with human immunodeficiency virus type 1 (HIV-1) infection and other STDs, number of sexual partners, sexual practices and recreational drug use.
Results: Overall, 7·6% of subjects tested were seropositive for HCV antibody. In univariate analysis, HCV infection was significantly associated with injecting drug use (IDU) (OR = 8·18, p < 0·0001) and HIV infection (OR = 3·14, p < 0·0001) and with self reported history of syphilis (OR = 1·88, p = 0·016), anogenital herpes (OR = 1·93, p = 0·017), gonorrhoea (OR = 2·43, p = 0·009) and hepatitis B (OR = 1·92, p = 0·010). In case control analysis, similar sexual behaviours (partner numbers and practices) were reported by HCV positive and HCV negative subjects except that HCV negative subjects *more* frequently reported engaging than HCV positive subject in unprotected receptive anal intercourse without ejaculation (OR = 0·61, p = 0·034), unprotected insertive (OR = 0·59, p = 0·039) and receptive (OR = 0·56, p = 0·016) oro-anal intercourse (rimming) and insertive fisting (OR = 0·48, p = 0·034). In multiple logistic regression analyses, only HIV-1 infection (OR = 3·18, p < 0·0001) and IDU in the previous six months (OR = 7·24, p < 0·0001) remained significantly associated with the presence of HCV antibody.
Conclusions: IDU was the major behavioural risk factor for HCV infection. If sexual or another form of transmission did occur, it may have been facilitated by concurrent HIV-1 infection.
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Keywords: hepatitis C; HIV; homosexual men

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Introduction

In the period since assays for antibody to hepatitis C virus (HCV) have become available,[1] the importance of blood contact, whether through the transfusion of blood products or the use of unsterilised injecting equipment has been established for the transmission of the virus.[2] On the other hand, the role of sexual transmission remains uncertain despite the fact that a number of studies have addressed this issue.[3–10]

In the past, homosexually active men have been identified as being at higher risk of sexually transmissible diseases (STDs) because of high rates of partner change and specific sexual practices. Some of the earliest and clearest evidence for sexual transmission of hepatitis A (HAV),[11] hepatitis B (HBV),[12] and hepatitis delta (HDV)[13] viruses arose from studies of homosexually active men. Sexual transmission of the aetiological agent of AIDS was similarly suggested by the initial recognition of the syndrome in homosexual men.[14]

Higher prevalences of HCV antibody have been consistently reported for homosexual men (3–19%)[5 15–23] than for volunteer blood donors (generally less than 1%),[24–27] suggesting that sexual transmission may have a role in the transmission of HCV infection. However, few studies of homosexually active men have examined the relationship between specific sexual behaviours and HCV infection rates[8 9 17 18 20 22] and then usually only considered receptive anal intercourse[8 9 17 18] or did not specify the particular practices studied.[22] In the remaining studies in homosexual men, only homosexuality *per se* or more general measures of sexual activity such as numbers of sexual partners, history of other STD, age, or years of homosexual activity were investigated as risk factors for HCV.

A history of STD correlated with the presence of anti-HCV antibody in a few studies[5 8 21] but not with others.[6 9 17 18 19 22] Similarly, relationships between HCV seropositivity and number of sexual partners have been weak[16 19 22] or non-existent.[7–9 17 18 20] Significantly, many of these studies did not systematically collect

information on injecting drug use.[5 15 17 22 23]

With a particular interest in sexual transmission, we sought to determine the prevalence of antibodies to HCV in a large cohort of homosexually active men in Sydney and to assess the relationship between HCV seropositivity and demographic and behavioural characteristics including particular sexual practices.

Subjects and methods

Between February 1984 and January 1985, 1075 homosexual or bisexual men were enrolled into the Sydney AIDS Prospective Study (APS), which aimed to identify risk factors associated with the development of AIDS.[28] APS subjects were recruited and monitored through several private and public primary care and STD services in central Sydney. At enrolment and at each six monthly review, subjects completed a self-administered questionnaire which examined sexual practices, use of recreational drugs and recent medical history. A physical examination was performed, and blood was drawn for determination of HIV-1 antibody status and T-cell subset enumeration. Serum was stored at $\leqslant 20°C$. At enrolment, APS subjects had a mean age of 36·0 years (range 17 to 67), 39·2% were seropositive for HIV-1 antibody and they reported a mean of 222 lifetime sexual partners.[28 29]

APS subjects were eligible for inclusion in the present analysis if there was sufficient stored serum available from any visit between 1984 and 1989 to test for antibody to HCV (n = 1038; 97%). For subjects with multiple stored serum samples, the most recent adequate sample was used.

Data on the number of lifetime sexual partners were derived from the questionnaire completed at enrolment. Specific sexual practices, use of recreational drugs and the diagnosis of other STDs were determined at baseline and at each six monthly visit. If the subject reported any of these factors at any time up to the visit corresponding to the stored serum sample that was tested for HCV antibody, he was coded as having a history of the factor. Data on injecting drug use (IDU) were limited to the period from six months before enrolment to the visit corresponding to questionnaire linked to the tested serum.

No information was sought on the receipt of blood transfusions or other blood products.

Serum samples were tested for antibodies to HCV by a first generation enzyme immunoassay (EIA) (Abbott Diagnostics, North Chicago IL). Of the initially HCV positive serum samples 67% were available for later testing by a third generation EIA (Abbott Diagnostics) together with a random sample of 50 initially negative samples. HIV-1 antibody status had been previously determined by EIA and confirmed by repeat EIA and Western blot.[29]

For categorical variables (sexual practices, history of STD, drug use) differences between subjects who were negative or positive for HCV antibody were analysed by Fisher's exact test. Odd ratios (OR) and 95% confidence intervals (CI) were calculated for each variable. For continuous variables (age, number of sex partners), differences were analysed by Wilcoxon's Rank Sum Test. Subjects with missing data for any variable were excluded from analyses involving that variable.

Multivariate analysis, using logistic regression, was performed using forward and backward stepwise selection methods. Statistical analyses were carried out using the SAS statistical package[30] and EGRET/PECAN.[31]

All serum samples were tested anonymously for HCV antibody by a unique study number allocated to participants at enrolment in the APS. The HCV study was approved by the Medical Ethics Review Committee, Faculty of Medicine, University of Sydney.

Results

Of the 1038 APS subjects for whom serum samples were available, 79 (7·6%) tested repeatedly positive for antibodies to HCV. A further six (0·6%) serum samples were borderline (within 20% of cut-off) on repeated testing, so were excluded from further analysis. Fifty three (67%) of the 79 initially positive samples were later retested using a third generation anti-HCV EIA of which all (100%) were confirmed as positive. Three (6%) of a sample of 50 initially negative specimens tested positive using the third generation assay. All of the analyses below are based on the results of testing with the first generation HCV antibody test.

There was no significant difference in age at the visit for which the tested sample was collected between HCV seronegative subjects (median 35 years; range 17–67) and HCV seropositive subjects (median 34 years; range 22–60) ($p = 0·574$). Tested serum was drawn a similar time after enrolment into the APS for HCV positive subjects (mean 107·7 weeks) and HCV negative subjects (119·9 weeks).

There was a significantly greater prevalence of antibody to HCV in the HIV-1 seropositive subjects (57 of 478; 11·9%) compared with the HIV-1 seronegative subjects (22 of 532; 4·0%) (OR = 3·14, $p < 0·0001$). However, there was no significant difference in the lifetime number of sexual partners reported by HCV seronegative subjects when compared with HCV seropositive subjects or in the number of partners in the previous six months (table 1).

Table 1 Reported number of sexual partners according to hepatitis C virus (HCV) antibody status

	HCV seropositive	*HCV seronegative*	*P*
Lifetime			
n*	79	953	
mean	388	358	
SD	430	390	
median	149	188	
range	0–1000	1–1000	0·996
Previous 6 months			
n*	62	706	
mean	4·7	7·2	
SD	6·1	12·1	
median	2·5	3·0	
range	0–30	0–100	0·211

*Number available for analysis. SD standard deviation.

Table 2 Sexual practices ever reported by subjects according to HCV serostatus

	HCV seropositive n = 79 (%)	HCV seronegative n = 953 (%)	P	OR (95% CI)
Insertive oro-penile	93·7	93·5	1·000	1·03 (0·40, 2·64)
Receptive oro-penile	93·7	91·5	0·672	1·38 (0·54, 3·50)
Insertive penile-anal	83·5	85·3	0·624	0·87 (0·47, 1·63)
Receptive penile-anal with ejaculation	68·4	70·7	0·700	0·89 (0·55, 1·47)
Receptive penile-anal without ejaculation	44·3	56·8	0·034	0·61 (0·38, 0·96)
Insertive oro-anal	31·7	43·9	0·039	0·59 (0·36, 0·96)
Receptive oro-anal	46·8	61·2	0·016	0·56 (0·35, 0·89)
Insertive fisting	12·7	23·3	0·034	0·48 (0·24, 0·94)
Receptive fisting	10·1	15·7	0·253	0·60 (0·28, 1·28)

Percentages provided are the number who ever reported the sexual practice/number available.

Table 3 Lifetime history of STD reported by subjects according to HCV serostatus*

	HCV seropositive (%)	HCV seronegative (%)	P	OR (95% CI)
Gonorrhoea	86·5	72·5	0·009	2·43 (1·23, 4·81)
Syphilis	52·3	36·8	0·016	1·88 (1·13, 3·13)
Anogenital herpes	61·3	45·1	0·017	1·93 (1·13, 3·27)
Hepatitis A	33·9	27·9	0·318	1·32 (0·77, 2·26)
Hepatitis B	55·7	39·6	0·010	1·92 (1·17, 3·14)
Non-gonococcal urethritis	61·8	66·1	0·508	0·83 (0·50, 1·38)
Enteric infection†	24·5	18·7	0·281	1·42 (0·73, 2·73)

Percentages provided are the number who reported a history of the STD/number responding to this question. *For HIV-1 infection see text; † amoebiasis, giardiasis, shigellosis.

HCV seropositive subjects were significantly *less* likely than negative subjects to report that they had engaged in receptive anal intercourse without ejaculation (withdrawal), receptive or insertive oro-anal intercourse (rimming) and insertive fisting. There was no significant difference between the two groups for the other reported sexual practices (table 2). HCV-seropositive subjects were significantly *more* likely to report a history of hepatitis B, gonorrhoea, anogenital herpes and syphilis than were HCV seronegative subjects (table 3).

HCV seropositive subjects were significantly more likely to report the use of almost all recreational drugs, both injected and non injected, than were their HCV seronegative counterparts (table 4). Both IDU and the sharing of injecting equipment were reported by a significantly greater proportion of HCV seropositive subjects than HCV seronegative subjects (table 4). Among the 39 subjects who reported IDU, 14 (36%) were HCV seropositive compared with only 63 (7%) of 920 subjects who did not report IDU.

Table 4 Drug use reported by subjects according to HCV serostatus

	HCV seropositive (%)	HCV seronegative (%)	P	OR (95% CI)
Marijuana	82·9	72·5	0·058	1·84 (0·99, 3·41)
MDA	44·6	72·5	0·008	2·17 (1·25, 3·77)
Amyl nitrate	75·0	64·1	0·071	1·68 (0·97, 2·92)
Ethyl chloride	24·0	9·3	0·002	3·08 (1·53, 6·21)
LSD	37·7	25·7	0·049	1·75 (1·02, 3·01)
Amphetamines	53·2	33·6	0·003	2·25 (1·34, 3·79)
Cocaine	45·2	26·9	0·003	2·24 (1·32, 3·78)
Heroin	19·2	4·2	0·0002	5·40 (2·46, 11·86)
Injecting drug use*	18·2	2·7	< 0·0001	8·18 (4·05, 16·51)
Shared injecting equipment*	17·3	2·4	< 0·0001	8·52 (4·10, 17·72)

Percentages provided are the number who reported a history of drug use/number responding to this question. *Limited to the period beginning six months before recruitment up to the time of collection of the specimen for HCV testing.

Table 5 Logistic regression analysis of factors associated with HCV seropositivity

Variable	Coefficient	P	OR	95% CI
HIV infection	1·16	< 0·001	3·18	1·88–5·38
Injecting drug use*	1·98	< 0·001	7·24	3·52–14·91

*At least once in previous six months.

Multivariate analysis

Each factor that was significantly associated with HCV at the univariate level was entered into a multivariate logistic regression model. Only two variables retained significance in this model: concurrent HIV-1 infection ($p < 0·001$) and a history of IDU ($p = 0·0041$) (table 5).

Discussion

Using a first generation test we detected HCV antibody in the serum of 7·6% of 1038 homosexually active men participating in a prospective study of the cause of AIDS through inner city health services. All available initially positive samples were confirmed using a third generation test but, based on the re-testing of a subset of 50 initially negative serum samples, the true prevalence of HCV antibody may have been higher. This prevalence rate was comparable with other studies of such men in developed nations and was higher than other populations in Australia such as blood donors (0·3%)[32] and antenatal patients (0·4%).[33]

Risk factors for HIV-1 infection in the same cohort have been reported previously.[34] Multivariate analyses confirmed that HIV-1 infection had the expected characteristics of an STD in that it correlated independently with receptive anal intercourse (with and without ejaculation) and with a history of syphilis, of gonorrhoea, and of hepatitis B. On univariate analysis, significant correlation were also observed between HIV-1 seropositivity and lifetime number of sexual partners and in the previous three months, insertive and receptive oral intercourse, insertive and receptive fisting, insertive and receptive oro-anal intercourse and insertive anal intercourse. Perhaps because the behaviour was relatively uncommon, IDU did not correlate with HIV-1 infection in this cohort.

The evidence for sexual transmission of HCV in this cohort was weak. We found that subjects with HCV antibody reported marginally *fewer* sexual partners than subjects without HCV antibody. By contrast, HIV-1 positive subjects reported significantly more sexual partners in their lifetime than HIV-1 negative subjects. Sexual transmission could also be indicated by association with particular sexual practices. Receptive anal intercourse has previously been identified as a major risk factor for the acquisition by homosexually active men of HBV and HIV-1 infections, both of which, like HCV, are blood-borne viruses. In our cohort a history of engaging in receptive intercourse with ejaculation was associated with HIV-1 infection but not HCV infection. Anal receptive intercourse without ejaculation (withdrawal) was reported *less* commonly by HCV positive than HCV negative subjects. By contrast, anal receptive withdrawal was

reported *more* commonly by HIV-1 positive than HIV-1 negative subjects. Three other sexual practices (insertive fisting, and insertive and receptive rimming) were also associated with a *negative* HCV antibody test at the univariate level. No specific practices were reported significantly more often by HCV seropositive subjects. These data, combined with the lack of association with hepatitis A and other enteric infections, also argue against any role for faeco-oral contact in the transmission of HCV infection.

One other cohort study of HCV in homosexual men, carried out in San Francisco, found associations between specific sexual practices and HCV seropositivity.[20] In this study, receptive anal intercourse, insertive and receptive fisting were all associated with HCV infection at the univariate level but only IDU retained significance in multivariate analysis (OR 6·4, 95% CI 3·2, 12·5).

In our study, HCV seropositive subjects were significantly more likely to report a history of gonorrhoea, syphilis, anogenital herpes and hepatitis B at the univariate level. However, these associations were not significant in multivariate analysis. By contrast, an association persisted in multivariate analyses between HIV-1 infection and a history of gonorrhoea, syphilis and hepatitis B, a finding that is expected for these "core group" STDs.

Remarkably, HCV antibody was found to correlate strongly and independently with the presence of HIV-1 infection even though HIV-1 infection in our cohort correlated with sexual behaviour and HCV infection did not. The association between these two viruses has been observed by others[4 7 9 35–37] and may be biological rather than behavioural.

One possibility is that the immune suppression caused by HIV-1 infection facilitates the transmission of HCV infection. Evidence for this hypothesis was suggested by the recently reported clusters of HCV infection among patients under treatment for haematological malignant disorders or severe aplastic anaemia despite strict observance of infection control procedures.[38] Sexual contact and direct blood contamination of medical equipment were shown to be unlikely explanations for these outbreaks. Enhanced transmission of HCV in association with HIV-associated immune suppression was also suggested by the differential transmission rates observed in studies of sexual partners of men with haemophilia[35] and of perinatal transmission of HCV.[36]

Another possible explanation for the association between HIV-1 and HCV infections is sexual practice selection according to the partners' HIV-1 status. It has been previously shown in a 1987 study of this cohort that HIV-1 seroconcordant couples were more likely to practice unprotected anal sex,[39] later termed "negotiated safety".[40] If HCV infection is sexually transmissible, however weakly, this phenomenon brings with it the hypothetical scenario of one dually-infected man (who may be more infectious for HCV than usual) unsafely exposing another immune compromised man (who may be more susceptible to HCV than usual). Data on sexual practices were insufficiently detailed for the whole cohort to test this hypothesis. Other non-sexual interactions between HIV-1 positive men could pose significant risks for HCV infection[38] which are yet to be determined. However, previous work has indicated that the presence of HIV-1 infection leads to more rapid loss of HCV antibody,[41] which would tend to mitigate against finding an association.

As expected, the presence of HCV antibody was independently associated with IDU: 18·2% of HCV seropositive and 2·7% of HCV seronegative subjects reported IDU. The contribution of IDU was probably an underestimate as the study questionnaires were limited to six months before enrolment. The univariate association between HCV antibody and a variety of non-injectable drugs hints at both under-ascertainment of IDU history and perhaps other lifestyle differences which could have a role in HCV transmission.

We conclude that IDU was the major behavioural determinant of HCV infection in this cohort of homosexually active men in Sydney in the 1980s. If sexual transmission played any role at all this may have been facilitated by concurrent HIV-1 infection. The possibility of other non-sexual, non-IDU risk factors for the transmission of HCV infection could not be excluded.

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