Hepatitis C virus infection in a male homosexual cohort: risk factor analysis

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Background: Hepatitis C virus (HCV) infection is a major cause of morbidity throughout the world. Parenteral exposure to infected blood accounts for the majority of cases. Sexual transmission is suggested by the higher prevalence of infection in sex workers and homosexual men. Sexual practices which contribute to HCV infection need to be identified.
Methods: The social and medical history, and HCV serostatus of 1058 homosexual men in the Pittsburgh arm of the Multicenter AIDS Cohort Study were analysed. Multivariate analysis was used to determine risk factors for HCV seropositivity.
Results: 31 men were HCV seropositive by enzyme immunoassay and recombinant immunoblot assay (2·9%). They were more likely to be HIV seropositive (39%) than the HCV seronegative men (19%). Needle sharing and illegal drug use were the most important risk factors for HCV seropositivity. Statistically significant sexual factors ($p < 0·05$) included a history of syphilis, rectal gonorrhea, anal insertive intercourse with ejaculation, and douche or enema use before anal receptive intercourse. The number of sexual partners was not a significant risk factor.
Conclusions: HCV infection is associated with specific sexually transmitted diseases (STDs) and sexual practices in the male homosexual population. The evidence of high risk behavior should be incorporated into ongoing educational efforts to decrease the incidence of STDs.
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Keywords: hepatitis C; STD; transmission

Introduction

Hepatitis C virus (HCV) infection has been well documented world-wide[1–11] and causes an estimated 150 000 to 170 000 incident cases annually in the United States. While the incidence of HCV is now about half of that of hepatitis B virus (HBV), HCV results in a substantially higher proportion (about 50%) of infected persons who develop chronic liver disease. The chronic sequelae of HCV infection include cirrhosis and hepatocellular carcinoma.[10–13] Moreover, coinfection with human immunodeficiency virus type 1 (HIV-1) may hasten the onset of cirrhosis[14] or liver failure[15] and thus increase future morbidity and mortality.

Intravenous drug use, blood transfusion, and occupational exposure to blood-borne pathogens are the major identifiable risk factors for HCV infection in the United States.[16 17] The risk of infection from sexual contact remains an important public health question. The emerging consensus is that sexual exposure has a limited role in the transmission of HCV.[18–25] For example, Bresters *et al*[18] studied 50 heterosexual partners of HCV viremic persons who had been in sexual relationships for a median of 13 years. None of the partners were HCV seropositive or viremic. The low rate of sexual transmission could be explained by the absence of HCV RNA in saliva or semen.[26]

Sexual transmission of HCV is difficult to delineate because sexual exposure is not always extricable from household contact and low socioeconomic class which are other known risk factors for HCV infection. The data which suggest that sexual transmission is epidemiologically important are from homosexual men and female sex workers who demonstrate a higher seroprevalence of HCV than the population at large.[20 22] Putative sexual risk factors reported to date include increased numbers of male homosexual partners with whom oral and anal intercourse were performed.[20] Interestingly, persons with sexually acquired HIV-1 infection do not have an increased risk of HCV infection in contrast to persons with parenterally acquired HIV-1 infection.[27]

Given the potential importance of sexual transmission of HCV, we sought to determine HCV seroprevalence and risk factors for HCV infection in a well-characterized cohort of sexually active homosexual men with relatively little intravenous drug use and infrequent history of blood transfusion. These population attributes may maximize the detection of sexual exposures related to acquisition of HCV infection. Information gained would be of use in counseling USA gay men regarding risk reduction strategies.

Methods

The Multicenter AIDS Cohort Study (MACS) is a longitudinal study of the natural history of HIV infection in homosexual and bisexual men.[28 29] This report focuses on 1062 volunteers enrolled at the University of Pittsburgh between April, 1984 and March, 1985. The recruitment methods and study design have been previously described.[28 29] Briefly, participants have undergone semi-annual visits for collection of epidemiologic data, physical examination, and procurement of plasma, serum, and peripheral blood

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Table 1 Baseline demographics and STD history

	HCV positive	HCV negative
Age (median, range) (years)	31·8 (20–59)	31·5 (18–69)
Race		
% white	28/3 (90%)	975/1020 (96%)
% non white	3/31 (10%)	45/1020 (4%)
Education		
< 12th grade	1/30 (3%)	16/998 (2%)
some college, no degree	21/30 (70%)	521/998 (52%)
4+ years college with degree	8/30 (27%)	461/998 (46%)
Transfusion (last 5 years)	2/38 (5%)	29/1017 (3%)
Lifetime STD history		
syphilis	10/31 (32%)†	111/1019 (11%)
gonorrhea	18/31 (58%)	402/1019 (39%)
urethral gonorrhea	17/31 (55%)	345/1014 (34%)
oral gonorrhea	4/30 (13%)	62/1009 (6%)
rectal gonorrhea	10/31 (32%)†	116/1013 (11%)
HIV seropositive	12/31 (39%)	195/1020 (19%)
Hepatitis B seropositive‡	23/31 (74%)*	531/1017 (52%)
RPR seropositive	4/31 (13%)	40/1017 (4%)

*p < 0·05.
†p < 0·01.
‡HBSAg+ or HBCAb+.

mononuclear cells for the establishment of a biological specimen bank.

Baseline serum samples were tested for antibody to HCV (anti-HCV) by enzyme immunoassay (EIA) (HCV 2·0, Abbott Park, North Chicago, IL). Initially reactive samples were repeated in duplicate. When one or both replicates were reactive, the sample was considered positive. Positive samples were further tested by the supplemental recombinant immunoblot assay (RIBA II, Ortho Diagnostics Systems, Inc., Raritan, NJ). Alanine aminotransferase levels (ALT) were determined on sera (Kodak Ektachem 700, Rochester, NY) from HCV seropositives and a matched group of HCV seronegative participants. Sera were also tested for HIV-1 antibody with the commercially available enzyme-linked immunosorbent assay (Genetic Systems, Seattle, WA). Anti-HIV-1 positive samples were confirmed by Western blot (Biorad, Richmond, CA). Serum antibody to hepatitis B core antigen and hepatitis B surface antigen was determined by commercial radioimmunoassay (Metpath Laboratories). Statistical analyses included both univariate 2 × 2 contingency tables, and stepwise multivariate logistic regression. Variables eligible for entry in the logistic regression were number of partners (0,1+) with whom receptive and insertive practices were performed (anal intercourse with ejaculation, oral intercourse, anilingus "rimming", dildo use, douche/enema usage), and the sexually transmitted diseases and recreational drug use variables that are listed in tables 1 and 2.

Table 2 Sexual practices and recreational drug usage history

	HCV positive	HCV negative
% reporting during prior 6 months:		
Insertive		
anal intercourse with ejaculation	27/31 (87%)*	703/1018 (69%)
rimming	18/31 (58%)	541/1018 (53%)
Receptive		
anal intercourse with ejaculation	24/31 (77%)	713/1018 (70%)
oral intercourse	29/31 (94%)	971/1017 (95%)
dildo usage	5/31 (16%)	132/1019 (13%)
douche/enema use	11/31 (35%)*	187/1018 (18%)
Drug usage (last 2 years)		
marijuana/hashish	27/31 (87%)	748/1019 (73%)
poppers/nitrates	23/31 (74%)	729/1019 (72%)
cocaine	18/31 (58%)*	380/1019 (37%)
heroine/methadone/opiates	3/31 (10%)†	12/1019 (1%)
amphetamines	18/31 (58%)†	340/1018 (33%)
% who shared IV needle (last 5 years)	9/31 (29%)†	17/1019 (2%)

*p < 0·05.
†p < 0·01.

Results

Samples were available on 1058/1062 (99·6%) men, 38 (3·6%) of whom were seropositive for HCV by EIA. The age, race, and education characteristics of the HCV EIA seropositive and seronegative groups were similar with a modest trend for less education in the HCV seropositive (table 1). These data reflect that the Pittsburgh MACS cohort is a predominantly white, well-educated group. Thirty one of the 38 (82%) men were HCV RIBA positive, while three men were RIBA indeterminate, and four were RIBA negative. Of the 31 men, 12 were HIV seropositive (39%).

The median ALT in the HCV EIA seropositives was 46 U/l (range 18–566 U/l). The median ALT of HIV seropositive and seronegative men was 48 and 53 U/l, respectively. This compared with a mean ALT in 68 matched HCV seronegative controls of 29 U/l (SD 15 U/l).

The lifetime prevalence of each sexually transmitted disease was higher in those with HCV infection, with syphilis and rectal gonorrhea exhibiting the largest differences between the groups ($p < 0·01$) (table 1). Consistent with this prior STD association and HCV infection, there were proportionally more HIV seropositive men among those with prevalent HCV infection (39%) than among the seronegative (19%). Serologic evidence of prior infection with both hepatitis B and syphilis (by Rapid Plasma Reagin) was also more common in those with HCV infection. These differences, however, did not reach statistical significance.

Insertive anal intercourse with ejaculation, and douche or enema use before anal receptive intercourse were also strongly associated ($p < 0·03$) with HCV seropositivity (table 2). Not surprisingly, needle sharing, and illegal drug use (opiates, and "uppers") were associated with HCV seropositivity (table 2). None of the HCV seropositive men had a history of blood transfusion.

Two multivariate logistic regression models for HCV seropositivity are shown in table 3. Model 1 includes those with a history of shared IV needle use, while model 2 excludes those with IV drug use history. With IV use in the model, this measure of parenteral exposure has the strongest association with HCV infection (odds ratio 24·8; 95% CI 9·2–66·5). Insertive anal intercourse was also significant (odds ratio 2·7; 95% CI 0·9–8·1). Not surprisingly, hepatitis B seropositivity has an odds ratio of 2·1 in this model; the seroprevalence

Table 3 Logistic regression analysis—HCV prevalent infection

	Adjusted Odds Ratio	95% Confidence Limits
Model 1		
Variable		
IV needle use	24·8	9·2–66·5
insertive anal intercourse	2·7	0·9–8·1
hepatitis B seropositivity	2·1	0·9–5·0
Model 2		
Variable		
insertive anal intercourse	4·1	1·0–17·8
RPR seropositive	3·5	1·0–12·5

Model 2 excludes 27 who reported shared IV exposure.

of hepatitis B is invariably higher in a needle sharing IV drug using community.

After excluding those with IV use, model 2 is quite similar to Model 1, as insertive anal intercourse and RPR seropositivity had similar odds ratios and confidence intervals.

Discussion

The data presented here provide evidence to support sexual transmission of HCV among homosexual men. Overall, these results show numerous univariate associations with HCV seropositivity including prior syphilis and gonorrhea (particularly rectal gonorrhea), insertive anal intercourse, and douche/enema usage. These indices of increased sexual activity among HCV seropositive men describe the general profile of increased probability of exposure to HCV infection.

The Pittsburgh MACS cohort is helpful for discriminating potential sexual HCV exposures from parenteral exposures because of the relative rarity of IV needle usage, a known mode of HCV transmission.[10 16] In fact, only 27/1057 (2·7%) of the entire Pittsburgh cohort had a history of shared needle use in the five years prior to entry. Despite the strong association between needle use and HCV seropositivity, only 9/31 (29%) of the HCV infected persons gave a history of needle use. Thus the proportion of HCV prevalent infections potentially attributable to sexual exposure is likely to be over 50% and perhaps up to 75%. This study presents the strongest evidence to date that STD and sexual practices are risk factors for HCV infection. In particular, there was still significant discrimination between HCV seropositive and seronegative men after the data were controlled for needle sharing. In fact, the exclusion of needle use clearly accentuates the importance of sexual markers for risk of HCV infection; these included RPR seropositivity and insertive anal intercourse. In contrast to the findings of Osmond *et al*,[20] the number of sexual partners was not a useful predictor of HCV seropositivity in this cohort of homosexual men.

The seroprevalence of HCV in the volunteer blood donor population in Pittsburgh is approximately 0·3% (Joseph Kiss, MD, personal communication). Thus, our well-educated male homosexual cohort had a 10-fold greater seroprevalence (31/1058; 2·9%) of HCV. The association with other sexually transmitted diseases, and well-defined sexual practices may lend insight into the mechanism of disease transmission.

A striking feature of the HCV EIA seropositivity in the cohort is the high concordance with positive supplemental test typically seen in persons with known risk factors for disease. While less than 50% of HCV EIA positive blood samples from volunteer blood donors are "confirmed" by RIBA,[30 31] 90% of hemophilics,[32] and 82% of our homosexual male cohort were positive by supplemental tests. This association was even stronger in HIV seropositive persons, all of whom were RIBA positive. The high incidence of ALT elevation in HCV seropositives further points to the serious nature of the HCV infection in this homosexual cohort. As previously noted, evidence suggests that HIV-HCV coinfection may accelerate HCV liver disease.[14 15]

Occasional reports of zidovudine (ZDV) hepatotoxicity[33 34] highlight the particular vulnerability to liver failure of the HCV-HIV seropositive patient on ZDV. It is unclear at this time whether the demonstration of sexual risk factors of HCV infection in a male homosexual cohort can be extended to the population at large. Additional studies are called for to corroborate the findings. There is little question, however, that testing and appropriate counseling should be available to at risk individuals. Populations with a high prevalence of HIV infection have an added impetus to contain the spread of HCV considering that the progression of liver disease is more rapid in the HIV seropositive.

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