Infection with HIV and hepatitis C virus among injecting drug users in a prevention setting: retrospective cohort study

Ingrid van Beek, Robyn Dwyer, Gregory J Dore, Kehui Luo, John M Kaldor

Abstract

Objectives: To estimate the incidence of HIV and hepatitis C virus and risk factors for seroconversion among a cohort of injecting drug users.
Design: Retrospective cohort study.
Setting: Primary healthcare facility in central Sydney.
Subjects: Injecting drug users tested for HIV-1 antibody (n = 1179) and antibodies to hepatitis C virus (n = 1078) from February 1992 to October 1995.
Main outcome measures: Incidence of HIV-1 and hepatitis C virus among seronegative subjects who injected drugs and underwent repeat testing. Demographic and behavioural risk factors for hepatitis seroconversion.
Results: Incidence of HIV-1 among 426 initially seronegative injecting drug users was 0.17/100 person years (two seroconversions) compared with an incidence of hepatitis C virus of 20.9/100 person years (31 seroconversions) among 152 injecting drug users initially negative for hepatitis C virus. Incidence of hepatitis C virus among injecting drug users aged less than 20 years was 75.6/100 person years. Independent risk factors for hepatitis C virus seroconversion were age less than 20 years and a history of imprisonment.
Conclusions: In a setting where prevention measures have contributed to the maintenance of low prevalence and incidence of HIV-1, transmission of hepatitis C virus continues at extremely high levels, particularly among young injecting drug users.

Introduction

Several studies have documented high prevalence of infection with hepatitis C virus among injecting drug users, both in industrialised[1–9] and developing countries.[10–12] Although longer duration of drug use has been consistently associated with higher prevalence of hepatitis C virus infection among this population,[1 3 5 12–16] high prevalence has also been reported among both young injecting drug users[3 17] and those who have been injecting for a relatively short time.[18] Studies of hepatitis C virus incidence have found high levels of transmission among current injecting drug users[1 5 19–23] and prison inmates,[5 24] but these studies have been based on relatively few seroconversions (1-10), limiting their potential to identify risk factors for newly acquired hepatitis C virus infection.

In Australia the extensive and continuing spread of infection with hepatitis C virus among injecting drug users has occurred in an environment where prevention strategies, including the wide implementation of needle and syringe exchange programmes since 1987, have contributed to the maintenance of a low prevalence (1-3%) and incidence of HIV.[1 3 5 25–27] We undertook a study of incidence of hepatitis C virus among injecting drug users attending Kirketon Road Centre, Sydney, with the major objective of identifying risk factors for newly acquired infection.

Methods

Kirketon Road Centre is a government funded facility in central Sydney established in 1987 to prevent and treat HIV/AIDS and other transmissible infections in young people, sex workers, and injecting drug users.[28]

In December 1991 testing for antibodies to hepatitis C virus became available in the context of clinical care at the centre, in addition to the existing provision of HIV screening. Hepatitis C virus testing was offered to all clients who reported a history of injecting drug use. All injecting drug users who underwent testing at the centre from February 1992 to October 1995 were included in the present study.

Standard HIV antibody testing was performed, including initial HIV enzyme linked immunosorbent assay (ELISA) with confirmatory western blot testing. Hepatitis C virus antibody testing was by the Monolisa R (ELISA) test, a second generation ELISA (Sanofi Diagnostics, Pasteur). All specimens positive for hepatitis C virus antibody underwent repeat testing. Only those who tested positive on second generation repeat testing were considered positive.

Information on demographic characteristics, sexual practice, and history of drug injecting were obtained from the client's medical file at the centre. This information was recorded by the clinical practitioner for all clients at the first visit and at the time of testing for HIV or hepatitis C virus. All behavioural information recorded at the first clinic visit referred to risk behaviour in the previous 12 months. Information recorded at the time of repeat testing for HIV or hepatitis C virus referred to risk behaviour in the previous 12 months or

Editorial by Coutinho

Kirketon Road Centre, PO Box 22, Kings Cross, New South Wales 1340, Australia
Ingrid van Beek, *director*
Robyn Dwyer, *research coordinator*
National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia
Gregory J Dore, *lecturer in epidemiology*
Kehui Luo, *statistician*
John M Kaldor, *deputy director, professor of epidemiology*
Correspondence to: Dr van Beek ivanbeek@ozemail.com.au

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Table 1 Characteristics of injecting drug users who underwent repeat testing for hepatitis C virus compared with those who had only one test

Characteristic	No (%) with repeat test (n=152)	No (%) with single test (n=420)	Odds ratio (95% CI)	P value
Sex:				
Men	63 (42)	181 (43)	1.0	
Women	85 (56)	234 (56)	1.0 (0.7 to 1.6)	0.83
Transsexual*	4 (3)	5 (1)	2.3 (0.4 to 11.0)	0.19
Age at test (years):				
<20	48 (32)	103 (25)	1.0	
20-29	96 (63)	254 (61)	0.8 (0.5 to 1.3)	0.32
⩾30	8 (5)	63 (15)	0.3 (0.1 to 0.6)	<0.001
Duration of drug use (years):				
<5	111 (73)	241 (57)	1.0	
⩾5	39 (26)	94 (22)	0.9 (0.6 to 1.4)	0.6
Unknown	2 (1)	85 (20)	0.1 (0.1 to 0.2)	<0.001
Type of drug used:				
Opiates only	20 (13)	39 (9)	1.0	
Stimulants only	46 (30)	108 (27)	0.8 (0.4 to 1.6)	0.57
Multiple drugs	74 (49)	177 (42)	0.8 (0.4 to 1.5)	0.49
Not known	12 (8)	95 (23)	0.2 (0.1 to 0.6)	<0.001
Shared equipment:				
No	62 (41)	176 (42)	1.0	
Yes	71 (47)	154 (37)	1.4 (0.9 to 2.1)	0.19
Not known	19 (13)	90 (21)	0.6 (0.3 to 1.1)	0.8
Sexual preference:				
Heterosexual	85 (56)	121 (29)	1.0	
Bisexual	32 (21)	43 (10)	1.0 (0.6 to 1.8)	0.87
Homosexual	35 (23)	33 (8)	1.5 (0.8 to 2.8)	0.14
Not known	0	223 (53)		
Methadone treatment:				
Never	117 (77)	130 (31)	1.0	
Ever	7 (5)	17 (4)	0.5 (0.2 to 1.2)	0.09
Not known	28 (18)	273 (65)	0.1 (0.1 to 0.2)	<0.001
History of imprisonment:				
No	112 (74)	182 (43)	1.0	
Yes	14 (9)	51 (12)	0.5 (0.2 to 0.9)	0.01
Not known	26 (17)	187 (45)	0.2 (0.1 to 0.4)	<0.001

*Men who were taking female hormone replacement therapy (with or without sex reassignment surgery) and who identified themselves as being transsexual.

since risk behaviour was last documented in the client's medical file (that is, since the first clinic visit or since the previous test visit), whichever was shorter. Periods of non-use between the age when clients started injecting and current age were subtracted in the estimation of duration of injecting drug use.

Analysis

Two separate statistical analyses were carried out. Incidence of HIV and hepatitis C virus infection was calculated by using the person years method[29] among clients initially seronegative for HIV antibody and hepatitis C virus antibody, respectively, who underwent repeat testing within the study period. Date of seroconversion was taken as the midpoint between the last negative and first positive antibody tests.

Because of the potential for confounding among some of these factors, we also carried out a survival analysis, using the method of proportional hazards regression. Each incident case of hepatitis C virus infection was matched with all members of the study population who initially tested negative for hepatitis C virus antibody within the same time period (3 months) as the first negative test in the cases but who remained negative on repeat test for a time period up to the estimated date of seroconversion in the case.[29]

To evaluate the possibility of selection bias in the hepatitis C virus incidence study we compared single and repeat testers among those who were initially negative for antibody to hepatitis C virus. Differences between these groups of subjects were examined for each of the risk factors considered in the study.

Results

Incidence of HIV-1

During the study period, HIV-1 antibody testing was carried out on 1179 clients who gave a history of injecting drug use. The overall prevalence of infection was 2.5%.

Among 426 injecting drug users initially negative for HIV-1 who underwent repeat testing, two seroconverted, giving an incidence of 0.17 per 100 person years (95% confidence interval 0.09 to 0.44). Median testing interval (time between first negative result and last negative or first positive result) was 12.5 (range 1-44) months. The number of HIV-1 antibody tests per client retested during the study period ranged from 2 to 11 (mean 3.3).

Incidence of hepatitis C virus

During the same period hepatitis C virus antibody testing was carried out on 1078 clients. The overall prevalence of infection was 45%.

Sixteen of the 1078 clients had indeterminate results and were excluded from further analysis. Among the 572 injecting drug users initially negative for hepatitis C virus antibody, 152 (27%) underwent repeat testing. Table 1 compares demographic and behavioural characteristics of those who had repeated tests (n = 152) and those who had a single test (n = 420). Those who had repeat tests were significantly younger and less likely to have been imprisoned, but there were no other significant differences between these populations. In particular, duration and type of drug use and history of needle sharing were similar between single and repeat testers.

Among the 152 injecting drug users who were initially negative for hepatitis C virus antibody and were retested, 31 were documented as having newly acquired infection during the study period, giving an incidence of 20.9 per 100 person years (13.5 to 28.3). For these 152 subjects the median follow up was 11.7 (range 1 to 42) months. The number of tests per client retested ranged from two to seven (mean 2.6). Median follow up among hepatitis C virus incident cases was 13.3 months compared with 11.2 months for other repeat testers.

The incidence of hepatitis C virus was higher among younger injecting drug users, with a rate of 75.6/100 person years for those under 20 years compared with 14.7/100 person years for those aged 20-29 years and 6.6/100 person years among injecting drug users 30 years or older (table 2). Other factors influencing incidence were type of drug used and needle sharing, with a higher rate among those who used more than one type of drug than those who used a single drug type and among those who reported needle sharing during the study period. Nine injecting drug users who reported that they had not shared needles were found to have acquired hepatitis C virus infection during the study period.

Table 2 Incidence of hepatitis C virus infection among injecting drug users

Variable	Seroconversions	Total	Incidence per 100 person years (95% CI)	P value
Overall number	31	152	20.9 (13.5 to 28.3)	
Sex:				
Men	15	63	26.2 (13.0 to 39.5)	
Women	14	85	15.9 (7.6 to 24.2)	0.18
Transsexual	2	4	70.3 (0.0 to 175.1)	0.19
Age at test (years):				
<20	13	31	75.6 (34.5 to 116.8)	
20-29	17	110	14.7 (7.7 to 21.6)	<0.0005
⩾30	1	11	6.6 (0.0 to 19.8)	0.02
Sexual preference:				
Homosexual	10	33	32.6 (12.4 to 52.7)	
Bisexual	5	35	12.6 (1.6 to 23.7)	0.08
Heterosexual	16	84	20.5 (10.5 to 30.6)	0.25
Duration of drug use (years):				
<5	21	100	22.9 (13.1 to 32.8)	
⩾5	10	51	17.9 (6.8 to 29.1)	0.52
Type of drug used:				
Opiates only	6	29	19.2 (3.8 to 34.6)	
Stimulants only	4	41	10.0 (2.5 to 19.9)	0.31
Multiple drugs	21	81	28.1 (16.1 to 40.1)	0.41
Shared equipment since last test:				
No	9	80	11.9 (4.1 to 19.8)	
Yes	22	72	30.2 (17.6 to 42.8)	0.02
Methadone treatment:				
Ever	6	27	18.0 (3.6 to 32.4)	
Never	20	117	18.0 (10.0 to 25.8)	0.99
History of imprisonment:				
Yes	12	25	60.8 (26.4 to 95.2)	
No	15	118	12.5 (6.2 to 18.8)	<0.0005
Study period:				
2/92 to 12/93	12	91	18.9 (8.2 to 29.5)	
1/94 to 10/95	19	125	22.5 (12.4 to 32.6)	0.63

Hepatitis C virus incidence was also substantially higher among injecting drug users who had been imprisoned (60.8/100 person years) than those who had not (12.5/100 person years). Sex, sexual preference, duration of drug use, and a history of methadone treatment did not significantly influence incidence. Hepatitis C virus incidence was similar in the two halves of the study period (18.9/100 person years for February 1992 to December 1993; 22.5/100 person years for January 1994 to October 1995).

There were no new hepatitis C virus infections among the four injecting drug users positive for HIV-1 who were negative for antibody to hepatitis C virus on initial testing and underwent repeat testing.

In the proportional hazards regression analyses, independent predictors of hepatitis C virus seroconversion were age less than 20 years and a history of imprisonment (table 3). A history of needle sharing was associated with an increase in risk that was of borderline significance (P = 0.06). Type of drug use was no longer significant in this adjusted model.

Discussion

We have shown an extremely high risk of hepatitis C virus infection among injecting drug users with continuing low prevalence and incidence of HIV infection who attend a primary healthcare service focused on the prevention of bloodborne infections. The risk of newly acquired hepatitis C virus infection was greatest among clients aged less than 20 years and those with a history of imprisonment. This study seems to be the largest so far carried out in terms of the number of recorded hepatitis C virus seroconversions and is consistent with previous reports from Australia,[1 5] Switzerland,[19] and Germany[21] in identifying a continuing high incidence of hepatitis C virus coincident with low incidence of HIV in injecting drug users.

Limitations of study

Several methodological issues need to be considered in the interpretation of these results. Although this study is the largest of incident hepatitis C virus cases reported in the literature to date, only 31 incident cases were observed, limiting the power of the analyses and the extent to which confounding can be excluded as an explanation of the observed associations. Despite this, our study had about 70% power (0.05% level) to detect a halving in incidence over the study period.

The high incidence among subjects recruited in this clinical setting may not be representative of hepatitis C virus incidence among injecting drug users more generally. As the centre provides HIV and hepatitis C virus prevention services, its clients may differ from injecting drug users who do not attend the centre. On the other hand, the centre's location in Kings Cross, a focus for the sex industry and drug trade in Australia, may result in the recruitment of injecting drug users at higher risk. Among injecting drug users who attended the centre, those who underwent repeat testing may not have been representative. Decisions by clients to undergo repeat HIV or hepatitis C virus testing may also have been influenced by perceptions of both client and clinician of

Table 3 Risk factors for hepatitis C virus seroconversion among injecting drug users

Variable	Odds ratio (95% CI)	P value
Sex:		
Men	1.00	
Women	0.94 (0.37 to 2.43)	0.91
Transsexual	4.26 (0.68 to 26.50)	0.12
Age at test (years):		
<20	2.47 (1.01 to 6.01)	0.04
20-29	1.00	
⩾30	0.61 (0.07 to 5.68)	0.67
Duration of drug use (years):		
<5	1.00	
⩾5	2.46 (0.97 to 6.19)	0.06
Type of drug used:		
Opiates only	0.95 (0.20 to 4.44)	0.95
Stimulants only	1.00	
Multiple drugs	1.07 (0.29 to 3.94)	0.92
Shared equipment:		
No or not known	1.00	
Yes	2.19 (0.96 to 4.99)	0.06
Sexual preference:		
Homosexual	1.00	
Bisexual	0.68 (0.17 to 2.67)	0.58
Heterosexual	0.69 (0.20 to 2.35)	0.55
Methadone treatment:		
Never	1.00	
Ever	1.08 (0.37 to 3.17)	0.89
Not known	3.99 (0.87 to 18.37)	0.08
History of imprisonment:		
No	1.00	
Yes	3.49 (1.35 to 9.02)	0.01
Not known	5.73 (1.48 to 22.15)	0.01

Key messages

- The prevalence and incidence of hepatitis C virus is high, while the prevalence and incidence of HIV remains low among injecting drug users
- Young age and history of imprisonment are risk factors for acquisition of hepatitis C virus infection
- HIV prevention strategies have been relatively ineffective in preventing hepatitis C virus infection in this population
- The role of imprisonment in the acquisition of hepatitis C infection should be further investigated

the client's risk behaviour. Those who underwent single or repeat tests for hepatitis C virus differed significantly in age and history of imprisonment from those who did not. The younger age of repeat testers may have biased upwards the overall estimate of hepatitis C virus incidence but should not affect the relation between age and risk of newly acquired hepatitis C virus infection, an extremely strong association in our study. In contrast, the lower proportion with a history of imprisonment among repeat testers could have biased downwards the overall estimate of hepatitis C virus incidence—but if all those who had an initial test had undergone repeat testing the association between imprisonment and newly acquired hepatitis C virus infection should have persisted.

Another methodological limitation is the dependence on self reports for information on injecting practice, particularly in a clinical context where the client may perceive an incentive to underreport risk behaviour to the attending clinician. Misclassification of variables has the effect of reducing the apparent size of any association, provided the extent of misclassification was not associated with hepatitis C virus status or the true values of the variables. There is no way to assess this issue on the basis of available data.

Incidence of hepatitis C

The extremely high incidence of hepatitis C virus among subjects under 20 years (76 per 100 person years) is a major public health concern. Younger injecting drug users could be at relatively higher risk of seroconversion compared with seronegative older injecting drug users if seronegativity becomes a marker of well established prevention practices with increasing duration of injection and age. Thus, increasingly lower risk cohorts of injecting drug users may be established with increasing age as those at higher risk are removed because of hepatitis C virus seroconversion. The 84% of injecting drug users under 20 years old who were negative for hepatitis C virus on initial testing presumably contains a higher proportion of high risk injecting drug users than the 26% of injecting drug users over 30 years old who were initially negative for hepatitis C virus. While prevalence studies indicate the cumulative impact of hepatitis C virus infection, only incidence studies can identify where infection is currently occurring and allow the direct assessment of the effectiveness of current prevention strategies.

The high incidence of hepatitis C virus coincident with low rates of HIV infection in the population may be due to two factors. Firstly, there is a high risk of hepatitis C virus transmission even for injecting drug users who only rarely share injecting equipment, simply because of the larger pool of hepatitis C virus infection compared with HIV infection among injecting drug users in Australia.[1 3 5 25] A second factor may be the apparent higher infectivity or transmissibility, or both, of hepatitis C virus compared with HIV per episode of blood contact.[30]

While there was a higher incidence of hepatitis C virus infection among injecting drug users who reported a history of sharing injecting equipment than those who did not, there were nevertheless cases of transmission in the latter group. Underreporting of risk behaviour may explain this finding, but also hepatitis C virus may be transmitted among injecting drug users in ways that do not involve the reuse of injecting equipment—for example, the sharing of items such as razors and toothbrushes, which may draw blood.

An important finding from the study was the strong relation between a history of imprisonment and the incidence of hepatitis C virus. We could not determine on the basis of available data whether the period of imprisonment was between the last negative and first positive test result in subjects who acquired hepatitis C virus infection. The observed association may be due to risk behaviour in prison or a consequence of an association between history of imprisonment and chaotic lifestyle, which may in turn be a surrogate marker of injecting risk behaviour. In either case, the association observed in this study population deserves further investigation, specifically to assess whether preventing the spread of hepatitis C virus should be better dealt with in the prison setting.

A recently published prospective cohort study among injecting drug users in another Australian state revealed a decline in incidence of hepatitis C virus, albeit non-significant, of 16.6 to 8.1/100 person years over the period 1990-5.[31] The absence of a similar decline in this study among an inner city population of injecting drug users already attending an HIV prevention service strongly suggests that current efforts aimed at the prevention of bloodborne viral transmission are inadequate to stem hepatitis C virus infection. The vulnerability of this population to hepatitis C virus may ultimately indicate the potential for HIV transmission.

Contributors: IB, chief investigator and guarantor of the study, initiated and coordinated the formulation of the primary study hypothesis and design of questionnaires, and participated in interpreting findings and writing the paper. RD participated in formulating the primary study hypothesis and designing questionnaires, coordinated data analysis and interpretation, and edited the paper. GJD participated in interpreting findings and writing the paper. KL participated in data analysis and interpretation. JMK participated in formulating the primary study hypothesis, designing questionnaires, and interpreting findings, and edited the paper.

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Mother to child transmission of hepatitis C virus: prospective study of risk factors and timing of infection in children born to women seronegative for HIV-1

Massimo Resti, Chiara Azzari, Francesco Mannelli, Maria Moriondo, Elio Novembre, Maurizio de Martino, Alberto Vierucci, and Tuscany Study Group on Hepatitis C Virus Infection in Children

Abstract

Objective: To determine the risk factors for and timing of vertical transmission of hepatitis C virus in women who are not infected with HIV-1.
Design: Follow up for a median of 28 (range 24-38) months of babies born to women with antibodies to hepatitis C virus but not HIV-1.
Subjects: 442 mothers and babies, of whom 403 completed the study.
Main outcome measures: Presence of antibodies to hepatitis C virus and viral RNA and alanine aminotransferase activity in babies. Presence of viral RNA, method of infection with hepatitis C, method of delivery, and type of infant feeding in mothers.
Results: 13 of the 403 children had acquired hepatitis C virus infection at the end of follow up. All these children were born to women positive for hepatitis C virus RNA; none of the 128 RNA negative mothers passed on the infection (difference 5%, 95% confidence interval 2% to 7%). 6 children had viral RNA immediately after birth. 111 women had used intravenous drugs and 20 had received blood transfusions. 11 of the infected children were born to these women compared with 2 to the 144 with no known risk factor (difference 7%, 2% to 12%).
Conclusions: This study suggests that in women not infected with HIV only those with hepatitis C virus RNA are at risk of infecting their babies. Transmission does seem to occur in utero, and the rate of transmission is higher in women who have had blood transfusions or used intravenous drugs than in women with no known risk factor for infection.

Introduction

Mother to child transmission of hepatitis C virus has been extensively studied in mothers with HIV-1 infection.[1–5] Previous reports have shown transmission rates ranging from 5.6% to 36%,[1 2 5] and the importance of HIV-1 coinfection in mothers has been repeatedly emphasised.[2 5] Little is known about the risk of mother to child transmission of hepatitis C virus or the correlates and timing of infection in children born to women who are HIV-1 seronegative. We conducted a multicentre prospective study to assess this.

Department of Paediatrics, University of Florence, 50132 Florence, Italy
Massimo Resti, *specialist in gastroenterology*
Chiara Azzari, *research paediatrician*
Francesco Mannelli, *specialist in infectious disease*
Maria Moriondo, *research fellow*
Elio Novembre, *paediatrician*
Alberto Vierucci, *professor of paediatrics*

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