European Journal of Epidemiology (2007) 22:183–193
DOI 10.1007/s10654-006-9089-7

INFECTIOUS DISEASES

Major decline of hepatitis C virus incidence rate over two decades in a cohort of drug users

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Accepted in revised form 17 November 2006

Abstract. Injecting drug users (DU) are at high risk for hepatitis C virus (HCV) and HIV infections. To examine the prevalence and incidence of these infections over a 20-year period (1985–2005), the authors evaluated 1276 DU from the Amsterdam Cohort Studies who had been tested prospectively for HIV infection and retrospectively for HCV infection. To compare HCV and HIV incidences, a smooth trend was assumed for both curves over calendar time. Risk factors for HCV seroconversion were determined using Poisson regression. Among ever-injecting DU, the prevalence of HCV antibodies was 84.5% at study entry, and 30.9% were co-infected with HIV. Their yearly HCV incidence dropped from 27.5/100 person years (PY) in the 1980s to 2/100 PY in recent years. In multivariate analyses, ever-injecting DU who currently injected and borrowed needles were at increased risk of HCV seroconversion (incidence rate ratio 29.9, 95% CI 12.6, 70.9) compared to ever-injecting DU who did not currently inject. The risk of HCV seroconversion decreased over calendar time. The HCV incidence in ever-injecting DU was on average 4.4 times the HIV incidence, a pattern seen over the entire study period. The simultaneous decline of both HCV and HIV incidence probably results from reduced risk behavior at the population level.

Key words: Hepatitis C virus, Hepatitis C incidence, HIV incidence, Parenteral drug abuse

Abbreviations: A C S = Amsterdam Cohort Studies (www.amsterdamcohortstudies.org); AIDS = Acquired immunodeficiency syndrome; 95% CI = 95% confidence interval; DU = Drug users (ever-injecting and never-injecting); ELISA = Enzyme linked immunosorbent assay; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus; IRR = Incidence rate ratio; NEP = needle exchange program; PY = person years

Introduction

The most important mode of hepatitis C virus (HCV) transmission is through exposure to infected blood [1, 2]. Therefore injecting drug users (DU) are at high risk for HCV infection. Their main route of transmission is the sharing of needles or other injecting equipment [3]. In this population, the reported prevalences of HCV range from 40% to 85% in Europe and North America [1, 4–11].

Under the threat of AIDS, DU reduced their injecting risk behavior and consequently their incidence of HIV infection in the mid-1980s [12, 13]. However, their HCV incidence appears to be less affected by this decreased risk behavior, perhaps because HCV is more transmissible than HIV. This hypothesis is confirmed by several studies that show a high and stable prevalence of HCV antibodies in this population [14–17]. In recent years, we reported a high but declining HCV prevalence among young DU in Amsterdam [18], whereas others still report high and stable HCV incidence among young DU who have recently started injecting [15, 17, 19, 20].

The open and ongoing Amsterdam Cohort Studies (ACS) among DU started in 1985, and stored serum was retrospectively tested for HCV antibodies.

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Therefore, the ACS has the unique potential to present HCV incidence data for DU over two decades. The objectives of our study were to measure the HCV incidence over this long period, to evaluate risk factors associated with HCV seroconversion, and to compare the HCV incidence to the HIV incidence in this cohort over the same period.

Materials and methods

The ACS is an open, prospective cohort study initiated to investigate the prevalence, incidence, and risk factors of infections with HIV-1 and other blood-borne and/or sexually transmitted diseases, as well as the effects of intervention [21]. The DU cohort was initiated in 1985; recruitment is ongoing and in recent years has been directed in particular to young DU.

Participation in the ACS is voluntary, and informed consent is obtained for every participant at intake. ACS participants visit the Health Service of Amsterdam every 4–6 months. At every visit, they complete a standardized questionnaire about their health, risk behavior, and socio-demographic situation. Questions about current behavior refer to the period between the present and the preceding ACS visit. Questions at baseline refer to the period since 1980 or since the start of regular use of hard drugs. Blood is drawn for laboratory testing and storage.

Laboratory methods

To study HIV prevalence and incidence, all ACS participants since 1985 (n = 1640) were prospectively tested for HIV antibodies by enzyme linked immunosorbent assays (ELISA), with confirmation by Western blot (since 1995: HIV Blot version 2.2, Genelab diagnostics).

To study the HCV prevalence and incidence, all participants with at least two visits between December 1985 and November 2005 (n = 1276) were retrospectively tested for HCV antibodies, using the first sample available in each case. Third generation ELISA tests were used to detect HCV antibodies (AxSym HCV version 3.0; Abbott, Wiesbaden, Germany). Individuals who were HCV-negative at ACS entry were tested for HCV antibodies at their most recent ACS visit. On finding HCV seroconversion, samples taken in between these two visits were tested to identify the moment of seroconversion.

Statistical analyses

The date of HCV or HIV seroconversion was estimated as the midpoint between the last seronegative and the first seropositive ACS visit. The median duration of the HCV seroconversion interval between visits was 4.0 months, interquartile range (IQR) 3.7, 5.1 months. Using the Kaplan–Meier method, we examined the time elapsed from the start of injecting drugs to HCV seroconversion. Only HCV-negative DU were included and they were considered to be at risk from their start of injecting. Those who had started injecting before ACS enrolment entered the risk set at their date of ACS entry (i.e., left truncation). Those who did not seroconvert or who were lost to follow-up were censored at their last ACS visit or ultimately 1 November 2005. We stratified the dates of starting injection into two decennia to investigate differences in HCV-free survival according to decade of starting injection.

Incidence rate curves were calculated by person-time methods. Poisson regression was used to test for the trend in HCV incidence over time and to determine risk factors for HCV seroconversion. All variables subject to change were treated as time-dependent variables. Due to the relatively long time-period between the point of infection and the appearance of HCV antibodies [22], the most probable moment of infection was assumed to have occurred around the last seronegative visit. Therefore, we assigned the risk behavior reported at that visit to the HCV seroconversion period. However, for nine participants who reported starting injection at the first HCV antibody-positive visit, we set back the report of injecting risk factors from this visit to the last HCV antibody-negative visit. Multivariate models were built using forward-stepwise techniques, and variables with a univariate p-value < 0.20 were considered as potential independent determinants. A p-value < 0.05 was considered statistically significant [23, 24]. Interactions in the final model were checked.

Variables related to general characteristics, drug use, and sexual risk behavior were examined as potential determinants of HCV seroconversion. General characteristics included sex, body mass index, calendar year of study visit, nationality, ethnicity, age, homelessness, hospitalization, and HIV status. The drug use variables included current injecting and the calendar period of starting injection. For current injectors, we also examined the frequency of injecting, the main type of drug injected, whether they injected mainly at home or borrowed needles, and needles obtained through a needle exchange program (NEP). Because there was a very strong association between current injecting and current borrowing of needles, we combined these two variables as follows: no current injecting; current injecting but no current borrowing of needles; current injecting and current borrowing of needles. Sexual behavior included having a steady sexual partner, injecting drug use of the steady partner, having unprotected sex (with an injecting partner), and current prostitution (women only).

To compare the HCV and HIV incidence, we assumed that the observed data (i.e., the number of

new infections per year) follows a Poisson distribution. We adopted a Bayesian approach. The logarithm of the incidence over calendar time was modeled using penalized splines. In this way, the incidence of both HCV and HIV was allowed to vary smoothly and nonlinearly over time [25–27]. If the trends have the same pattern, then the difference between the incidences on a logarithmic scale is a constant.

Results

General characteristics and HCV prevalence

In total, 1640 DU have been enrolled in the ACS since December 1985. Of these, 1259 DU met the follow-up criteria of at least two visits before November 2005 and also had enough stored serum to allow HCV testing. Of these participants, 803/1259 (63.8%) were male and 937/1259 (74.5%) had a Dutch nationality. The median age at ACS entry was 30.5 years (IQR 26.5, 35.8) (Table 1).

Of the 1259, 952 participants were ever-injectors: DU who had ever injected drugs before entry (n = 905) or who had started injecting drugs during follow up (n = 47). The median age at start of injection was 21.7 years (IQR 17.8, 26.0).

The median ACS follow-up time for ever-injectors was 7.3 years (IQR 3.8,12.6), whereas it was 5.4 years (IQR 2.6, 10.4) for never-injectors. In ever-injectors, the main drugs recorded at ACS entry were a cocktail of heroin and cocaine (40.0%), and most participants had injected daily or more frequently in the preceding 6 months (34.0%).

Of the 1259 DU, 803 (63.8%) had HCV antibodies at entry; of these, 30.6% (246/803) were HIV-co-infected. The prevalence at entry of HCV antibodies in ever-injectors varied from 92.9% in 1986 to 69.2% in 2001. The prevalence among never-injectors was 6.5% over the total study period and varied from 0% to 22.2% per calendar year.

When evaluating HCV prevalence at entry by the time elapsed since start of injection, such prevalence was 59/99 (59.6%) for participants who had injected for less than 2 years before entry vs. 137/164 (82.5%) for participants who had injected for 3–5 years before entry. Among participants with >10 years of injecting drug use before ACS entry, the HCV prevalence was 327/346 (94.5%).

Table 1. General characteristics of drug users in the Amsterdam Cohort Study

	Total	Ever-injecting DU	Never-injecting DU
Total number of participants	1259	952	307
Median age[a] (IQR)	30.5 (26.5, 35.8)	29.84 (26.0, 36.0)	30.6 (26.8, 35.7)
% Male sex	63.8	61.3	71.3
% Dutch nationality	74.7	86.0	71.0
Median duration of follow-up (IQR)	6.95 (3.56, 12.1)	7.33 (3.84, 12.6)	5.41 (2.60, 10.4)
Median age at start of injecting drugs (IQR)	–	21.7 (17.8, 26.0)	–
Main drugs injected (%)[a]	–		–
Cocktail, heroin/cocaine		40.0	
Heroin		12.2	
Cocaine		8.9	–
Main other drugs used (%)[a]	–		–
Cocktail, heroin/cocaine		4.4	41.0
Heroin		31.5	43.0
Cocaine		26.7	4.2
Frequency of injecting (%)	–		–
No current injecting		28.5	
Daily		34.0	
Weekly		30.7	
Monthly		4.4	
Number of recently borrowed needles(%)[a]	–		–
0		44.9	
1–10		7.6	
>10		0.9	
Unknown		46.4	
% HCV-antibody positive[a]	63.8	82.2	6.5
HCV seroconversions during follow-up	59	58	1
% HIV-positive[a]	20.4	25.8	3.6
HIV seroconversions during follow-up	95	90	5

Ever-injecting DU: DU who had injected before ACS entry (n = 905) or started injecting during follow up (n = 47).
Current/recently: in previous 6 months.
[a]At entry.

HCV incidence

Of the 456 DU seronegative for HCV at ACS entry, 59 seroconverted during follow-up, of whom 58 injected and 1 did not. Among ever-injectors, the incidence declined from 27.5/100 PY in the late 1980s to approximately 2/100 PY in recent years (Figure 1a). There was a significant downward trend in HCV incidence over calendar time (IRR 0.86 per calendar year; 95% CI 0.82, 0.90, $p < 0.001$) (Figure 1a).

In line with the decline of the HCV incidence, the time since starting injection until HCV seroconversion has lengthened in more recent calendar periods. In 1980–1989, the median interval was 2.27 years (IQR 1.2, 5.6 years), whereas in 1990–1999, the median was 9.10 years (IQR 2.1, ∞ years) (Figure 2).

When restricting our analysis to DU who reported injecting since the preceding visit, a higher incidence but similar pattern was observed. In 1985–1990, the incidence rate in this group was extremely high, between 50–80/100 PY, but it dropped to 5–10/100 PY in 1990–1999.

Comparison of HCV and HIV incidence

Of 1276 DU, those HIV-negative at entry numbered 1013, of whom 95 (including 90 ever-injectors) seroconverted for HIV during follow-up. The HIV incidence rate among ever-injectors dropped from 8.52/100 PY in 1986 to approximately 0 since 2000, with a slight increase in 2005 (Figure 1b).

When the observed HCV and HIV incidence curves and their fitted smooth curves are plotted in one graph with two scales, the curves look similar in shape. When we plotted the differences between the logs of the fitted model, we found no convincing evidence for a difference in pattern. The mean value of the differences on a log-scale over the twenty years is 1.48; hence the scale factor is estimated to be 4.4 (data not shown). The observed and fitted incidence patterns for both HCV and HIV with 95% confidence intervals are shown in Figure 1c.

Risk factors for HCV seroconversion

Time since start injecting can be seen as a proxy for the duration of exposure time, and preliminary analysis showed a very strong association between time since start of injecting and the timepoint of HCV seroconversion (IRR 0.80 per year), 95% CI 0.74, 0.86) (Table 2). Therefore, in bivariate analysis, to adjust for variation in time from start of injecting (and thus time of exposure), all other variables were adjusted for time from start of injecting as a time-updated variable.

After correction for time since starting injection, the following risk factors were found to be significantly associated with an increased risk of HCV seroconversion: the combined variable of current injecting and current borrowing of needles, earlier calendar year of visit, use of NEP, type of drugs injected, frequency of injecting drug use, and earlier decennium of starting injection (Table 2). Interestingly, in univariate analysis persons were more at risk for HCV if they had seroconverted for HIV (IRR 5.68; 95% CI: 2.27, 14.2) or were chronically infected with HIV (IRR 3.12; 95% CI: 0.76, 12.8) than if they were HIV-negative. The type of drugs injected, and frequency of injection were associated with an increased risk of HCV infection, their effect is attributable to current injecting drug use itself. In fact, when evaluating these variables among only DU injecting drugs within the past 6 months we found no association between NEP use, the type of drug injected, or injection frequency and HCV infection.

In multivariate analysis, we found that current injecting combined with current borrowing of needles was a major risk for HCV seroconversion; the IRR was 29.9 (95% CI: 12.6, 70.9) for current injecting and borrowing compared to no injecting in the preceding period. The longer the time between start of injecting and study visit, the smaller the risk of HCV infection: IRR 0.89; 95% CI: 0.83, 0.96) (Table 2). Calendar year remained significantly associated with a decreased risk of HCV infection when it was evaluated continuously in the model (IRR 0.87; 95% CI: 0.82, 0.93).

Discussion

This study describes the prevalence and incidence of HCV in a large group of DU in Amsterdam, the Netherlands, over two decades. Findings show that the HCV incidence dropped considerably in that period. Interestingly, when we compared the HCV incidence rate to the HIV incidence rate in the same group of DU that have ever injected, the decrease was similar for the two infections. In line with the decline of the HCV incidence, the time from the start of injecting drugs until HCV seroconversion is longer at present than in the past.

To our knowledge, this is the first study to document among DU, over such a long period, a decline in HCV incidence that is not only strong but also comparable to the decline in HIV incidence. Our finding of a decline in HCV incidence contrasts with other studies that show a stable HCV incidence [19, 28]. One explanation may be that those studies analyzed the HCV incidence over a shorter time interval, which might have been insufficient to show a significant decline. In Baltimore, USA, a significant decline of the HCV incidence was found in injecting DU followed between 1988 and 1996, but in contrast to our study with ongoing recruitment of participants, this decline was observed in a closed cohort study and a saturation effect probably has contributed to this decline [29].

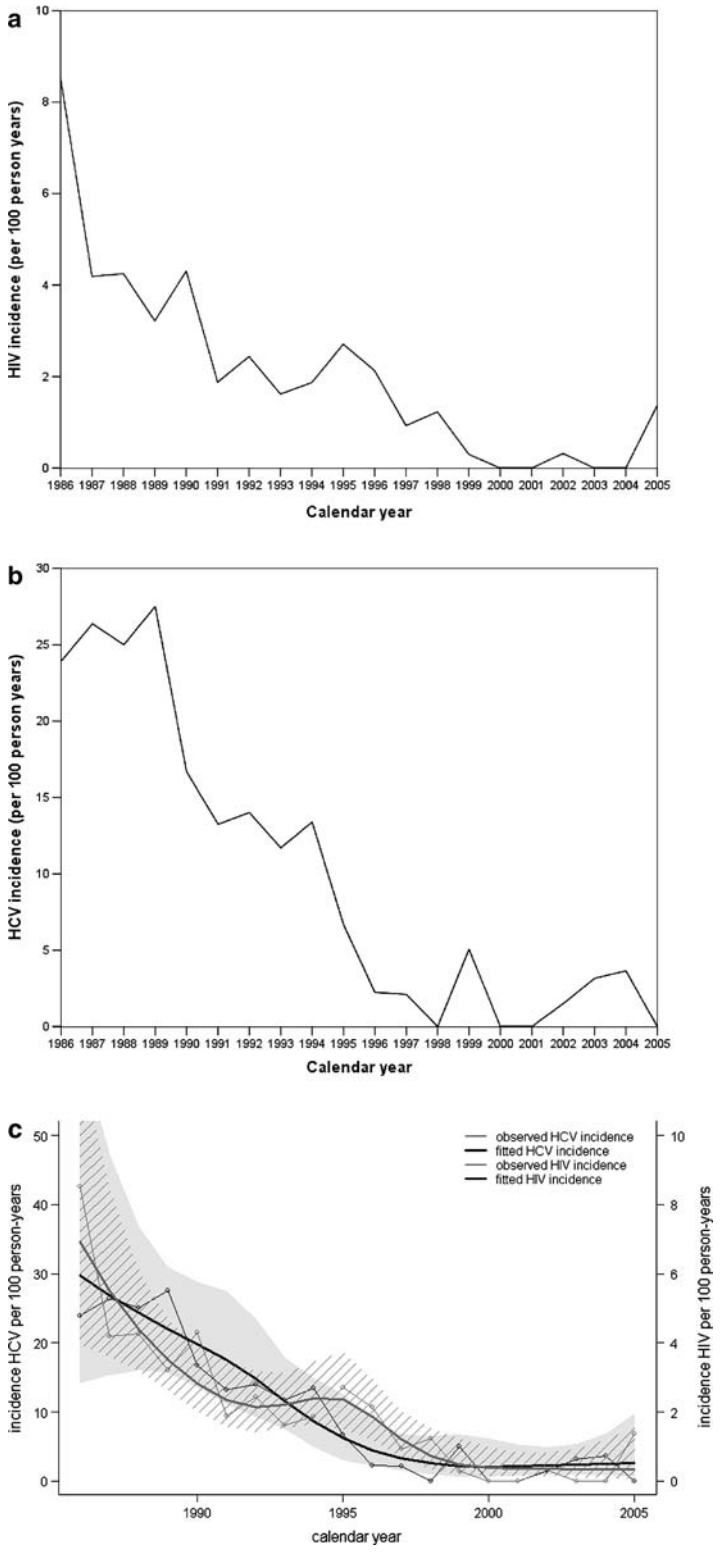

Figure 1. (a, b) Observed HIV and HCV incidence curves among ever injecting DU in the ACS (1985–2005); (c) observed and fitted HCV (left *y*-axis) and HIV (right *y*-axis) incidence curves among ever injecting DU in the ACS (1985–2005).

In addition, the risk behavior of the total group of DU included in the ACS has substantially declined over time in Amsterdam [30]. This finding suggests that a decline in risk behavior at the population level has contributed to the simultaneous decline of HCV and HIV incidence. The decreasing HCV incidence in Amsterdam DU, as opposed to high incidences in DU elsewhere, may likewise be partly explained by a larger reduction in injecting risk behavior in Amsterdam, compared to reductions elsewhere. The

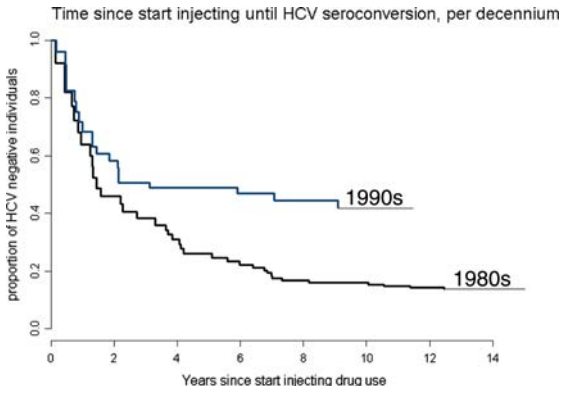

Figure 2. Kaplan–Meier estimates of the cumulative proportion of DU who remain without HCV infection since starting injection, grouped per decennium: the 1980s (lower line) and 1990s (upper line). Curves were truncated when fewer than 10 persons remained at risk for HCV (thin line). Persons who started injecting before 1980 or after 2000 are not depicted in this figure, because at any moment in those periods, less than 10 persons were at risk for HCV.

impact of methadone provision and NEP on this decline of risk behavior is very important and should be a focus of future studies. Methadone and NEP were readily available throughout the study period, and the median prescribed daily methadone dose increased during this period. Murray et al. [31] demonstrated by mathematical modeling that the level of risk behavior determines whether HCV incidence decreases. They calculated that if injecting risk behavior is sufficiently decreased (through intense NEP and/or harm reduction strategies), then HCV incidence will accordingly decline.

Mathematical models have additionally shown the natural course of an epidemic might bring a decline in the incidence of infection [32]. When a new infectious agent enters a population, the number of infected individuals and the incidence soon increase. Thereafter, as the number of susceptibles decreases, the chance for an infected individual to come into contact with an uninfected individual decreases as well. When the density of uninfected persons reaches a threshold below which the number of susceptibles cannot sustain an ongoing epidemic, incidence peaks and then starts to decline. In this light, the decrease in HIV incidence observed shortly after the introduction of HIV in Amsterdam in the early 1980s was due to the depletion of susceptibles, along with a reduction in risk behavior. However, such depletion is less likely to be the case for HCV, which has existed among DU since the 1960s and possibly even before [33, 34]. This implies that the decrease in injecting risk behavior might have an even greater impact on HCV than on HIV.

The contrast in study findings may be explained in part by the HCV test used. We used third-generation ELISA tests to measure HCV antibodies, whereas studies from the late 1980s/early 1990s used first- or second-generation ELISA tests, which were more inclined to give false positive test results [35].

The HCV prevalence among DU at ACS entry varies between 70% and 90%, with lower prevalence rates in recent years. This is consistent with what was described among DU in Amsterdam in the early 1990s [28] and among recently starting injectors in Amsterdam and elsewhere [18, 36]. The HCV prevalence in never-injecting DU is much lower than in ever-injectors but still much higher than in low-risk populations (e.g., blood donors) or the general populations in Western countries [1, 37], household transmission, rare sexual transmission, and reliability/unreliability of answers given in interviews may contribute to this finding among never-injecting DU.

Among DU in Amsterdam who have injected in the past 6 months, incidence rates were extremely high in the 1980s (50–80/100 PY). Similarly high incidence rates have been described by Smyth et al. among young, DU who have recently started injecting in Ireland, in the 1990s [10].

A possible limitation of our study is its lack of confirmatory testing for positive results of HCV antibody testing. However, such results in a high-risk population are likely to be true positives [35], and 232/803 (28.9%) of the positive participants were tested at two study visits or more, all with consistent HCV-positive test results. Therefore we believe the lack of confirmatory testing did not influence our results. Furthermore, although the ACS is an open, prospective cohort study, the influx of new participants in recent years has been lower than in earlier years. Lower risk DU could be overrepresented due to the decease of high-risk DU. However, the most recent HCV seroconversions took place in young DU who entered the cohort after 1994.

Our risk factor analysis showed that HCV seroconversion is associated not only with current injecting and borrowing needles, as expected, but also with calendar year and time since start of injecting. The majority (70%) of HCV infections could have been prevented by eliminating the borrowing of needles. This might partly reflect the effect of the use of NEP, which were always available during the study period, but individual factors also might play a role in the decision to use NEP.

In conclusion, HCV incidence in our cohort showed a sharp decline in the past two decades, similar to the decline in HIV incidence, most likely due to a decrease in injecting risk behavior. We found that those who started injecting in a recent calendar period are at lower risk of HCV infection, presumably due to prevention activities. Thus it is important to continue and enhance such activities among DU and others at risk of starting injection, especially because the HCV risk is highest just after the start of injecting, when probably injectors are inexperienced.

Although we did not find an independent effect from either participation in a methadone program or

Table 2. Univariate, bivariate, and multivariate IRR of potential risk factors for HCV infection

	Univariate analysis						Bivariate analysis*			Multivariate analysis		
	HCV sc	PY	Incidence rate (per 100 PY)	IRR	95% CI	*p* Value	IRR	95% CI	*p* Value	IRR	95% CI	*p* Value
Methadone dosage												
0 mg	34	408	8.33	2.23	(0.68, 7.26)	0.18	1.07	(0.33, 3.51)	0.92			
1-59 mg methadone	20	358	5.59	1.49	(0.44, 5.02)		0.95	(0.28, 3.21)				
>60 mg	3	80	3.75	1			1					
HIV status												
HIV-negative	51	831	6.14	1		0.006	1		0.25			
HIV primary infection	5	14	35.7	5.68	(2.27, 14.2)		2.18	(0.85, 5.57)				
HIV chronically infected	2	10	20.0	3.12	(0.76,12.8)		1.95	(0.47, 8.07)				
Decennium of starting injection												
1970-1979	1	146	0.68	1		0.002	1		0.13	**		
1980-1989	37	443	8.35	12.2	(1.67, 88.9)		1.56	(0.19, 12.6)				
1990-1999	19	239	7.95	11.6	(1.55, 86.6)		1.01	(0.12, 8.37)				
2000-present	1	23	4.35	6.26	(0.39, 100.0)		0.32	(0.02, 5.74)				
Use of NEPs												
No current injecting	10	623	1.61	1		<0.001	1		<0.001			
Current injecting, no NEP	18	92	19.6	12.3	(5.66, 26.6)		7.61	(3.43, 16.8)				
Current injecting, irregular NEP	11	36	30.6	19.1	(8.09, 44.9)		8.40	(3.39, 20.8)				
Current injecting, always NEP	19	99	19.2	11.9	(5.53, 25.6)		7.87	(3.58, 17.3)				
Age (per 10 years)	58	856	6.78	0.45	(0.31, 0.65)	<0.001	0.87	(0.59, 1.26)	0.45			
Type of drugs mainly injected												
No current injecting	10	623	1.61	1		<0.001	1		<0.001			
Heroin	9	46	19.8	12.2	(4.97, 30.1)		7.18	(2.86, 18.0)				
Cocaine	10	41	24.4	15.2	(6.31, 36.4)		8.69	(3.53, 21.4)				
Cocktail, heroin/cocaine	21	115	18.3	11.4	(5.37, 24.2)		6.51	(2.99, 14.2)				
Amphetamines	2	17	11.8	7.46	(1.64, 34.1)		3.81	(0.82, 17.6)				
Methadone	3	9	33.3	21.3	(5.87, 77.5)		35.5	(9.7, 129.5)				
Other/unknown	3	4	75.0	44.6	(12.3, 162.2)		25.6	(7.00, 93.5)				
Frequency of injecting												
No current injecting	10	623	1.60	1		<0.001	1		<0.001			
More times per day	17	49	34.7	21.7	(9.92, 47.3)		10.4	(4.54, 23.9)				
Once daily	1	4	25.5	15.9	(2.03, 124.3)		12.2	(1.55, 95.9)				
More times per week	19	66	28.8	18.0	(8.36, 38.6)		10.5	(4.75, 23.3)				

Table 2. Continued

	Univariate analysis						Bivariate analysis*			Multivariate analysis		
	HCV sc	PY	Incidence rate (per 100 PY)	IRR	95% Cl	*p* Value	IRR	95% Cl	*p* Value	IRR	95% Cl	*p* Value
Once weekly	1	12	8.23	5.13	(0.66, 40.1)		5.27	(0.67, 41.2)				
More times per month	3	37	8.13	5.07	(1.40, 18.4)		2.71	(0.72, 10.1)				
Once monthly	2	13	15.2	9.46	(2.07, 43.2)		8.18	(1.79, 37.4)				
Less than once monthly	4	48	8.36	5.21	(1.63, 16.6)		4.19	(1.31, 13.4)				
Frequency of non-injecting drug use												
More times per day	21	249	8.43	0.73	(0.25, 2.14)	0.35	0.60	(0.20, 1.74)	0.39			
Once daily	2	38	5.26	0.45	(0.08, 2.48)		0.45	(0.08, 2.47)				
More tomes per week	16	235	6.81	0.59	(0.20, 1.77)		0.60	(0.20, 1.80)				
Once weekly	2	68	2.94	0.25	(0.05, 1.39)		0.20	(0.04, 1.09)				
More times per month	2	47	4.26	0.37	(0.07, 2.03)		0.47	(0.09, 2.58)				
Less than once monthly	0	17	0.00	1			1					
Type of drugs mainly used (non-injecting)												
Heroin	20	311	6.43	1		0.98	1		0.81			
Cocaine	24	332	7.23	1.12	(0.62, 2.03)		1.33	(0.73, 2.41)				
Cocktail heroin/cocaine	2	32	6.25	0.96	(0.22, 4.11)		1.07	(0.25, 4.58)				
Amphetamines	1	13	7.69	1.16	(0.16, 8.66)		1.48	(0.20, 11.0)				
Having a steady partner												
No	36	496	7.26	1.19	(0.70, 2.02)	0.52	1.55	(0.91, 2.64)	0.10			
Yes	22	360	6.11	1			1					
Injecting drug use of the steady partner												
No	12	255	4.71	1		0.10	1		0.99			
Yes	10	105	9.52	2.04	(0.88, 4.71)		0.99	(0.42, 2.33)				
Homelessness												
No	52	800	6.50	0.61	(0.26, 1.43)	0.29	0.67	(0.29, 1.57)	0.39			
Yes	6	57	10.5	1			1					
Hospitalized in past 6 months												
No	56	817	6.85	1.34	(0.33, 5.50)	0.67	1.36	(0.33, 5.59)	0.65			
Yes	2	39	5.13	1			1					
Current prostitution (females only)												
No	24	243	9.88	1		0.19	1		0.82			
Yes	2	47	4.26	0.43	(0.10, 1.81)		1.19	(0.28, 5.07)				

Table 2. Continued

	Univariate analysis						Bivariate analysis*			Multivariate analysis		
	HCV sc	PY	Incidence rate (per 100 PY)	IRR	95% CI	*p* Value	IRR	95% CI	*p* Value	IRR	95% CI	*p* Value
Current injecting and borrowing needles												
No current injecting	10	623	1.61	1		< 0.001	1		< 0.001	1		< 0.001
Current injecting, no current borrowing of needles	25	159	15.7	9.80	(4.71, 20.4)		6.26	(2.94, 13.3)		8.70	(4.03, 18.8)	
Current injecting and current borrowing of needles	12	23	52.2	32.7	(14.1, 75.7)		21.4	(9.17, 50.1)		29.9	(12.6, 70.9)	
Time since start of injecting	58	856	6.8	0.80	(0.74, 0.86)	< 0.001				0.89	(0.83, 0.96)	< 0.001
Year of visit	58	856	6.8	0.86	(0.82, 0.90)	< 0.001	0.94	(0.89, 0.99)	0.009	0.87	(0.82, 0.93)	< 0.001
Sex												
Male	32	566	5.65	1		0.085	1		0.36			
Female	26	290	8.97	1.59	(0.95, 2.66)		1.28	(0.76, 2.16)				

* Adjusted for time since start of injection.
** Analyses were not adjusted for time since start of injection and decennium of start, because the decennium can be derived from the time since start of injection and calendar year of visit.

from the use of NEP, these prevention measures in combination are likely to have contributed to the decline in risk behavior related to drug use at the population level. Therefore, it is important to evaluate the possibilities for harm reduction worldwide. During the late 1980s many acute HCV infections occured, so there might have been more DU with high HCV RNA levels associated with acute HCV infection. Therefore, in that period there may have been more and/or easier transmission of HCV. Higher HCV RNA levels have also been associated with HIV co-infection [38]. However, we believe that because the HCV prevalence remained relatively high and the pattern of the HIV and HCV incidence was comparable during the study period, on population level the HCV RNA level varied only little over time, also because treatment prescription for HCV was very limited in our cohort.

Finally, it is important to decrease the prevalence of chronic HCV carriers and thus reduce the possibility for HCV transmission. DU should therefore be systematically screened for HCV infection, and those chronically infected should be treated [39].

Acknowledgments

The authors would like to thank J. Bax and A. Snuverink for data collection and blood sampling; all subjects for study participation; M. Xiridou for her contribution to the manuscript, and L. Phillips for the editing of the manuscript. *Financial support*: The ACS Amsterdam Cohort Studies on HIV infection and AIDS, a collaboration between the Amsterdam Health Service, the Academic Medical Center of the University of Amsterdam, Sanquin Blood Supply Foundation and the University Medical Center Utrecht, are part of the Netherlands HIV Monitoring Foundation and financially supported by the Netherlands National Institute for Public Health and the Environment.

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