Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users

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ABSTRACT

Objectives To investigate the impact of harm-reduction programmes on HIV and hepatitis C virus (HCV) incidence among ever-injecting drug users (DU) from the Amsterdam Cohort Studies (ACS). Methods The association between use of harm reduction and seroconversion for human immunodeficiency virus (HIV) and/or hepatitis C virus (HCV) was evaluated using Poisson regression. A total of 714 DU were at risk for HIV and/or HCV during follow-up. Harm reduction was measured by combining its two most important components—methadone dose and needle exchange programme (NEP) use—and looking at five categories of participation, ranging from no participation (no methadone in the past 6 months, injecting drug use in the past 6 months and no use of NEP) to full participation (≥ 60 mg methadone/day and no current injecting or ≥ 60 mg methadone/day and current injecting but all needles exchanged). Results Methadone dose or NEP use alone were not associated significantly with HIV or HCV seroconversion. However, with combination of these variables and after correction for possibly confounding variables, we found that full participation in a harm reduction programme (HRP) was associated with a lower risk of HIV and HCV infection in ever-injecting drug users (DU), compared to no participation [incidence rate ratio 0.43 (95% CI 0.21–0.87) and 0.36 (95% CI 0.13–1.03), respectively]. Conclusions In conclusion, we found that full participation in HRP was associated with a lower incidence of HCV and HIV infection in ever-injecting DU, indicating that combined prevention measures—but not the use of NEP or methadone alone—might contribute to the reduction of the spread of these infections.

Keywords Harm reduction, hepatitis C virus, HIV, injecting drug use, methadone, needle exchange programmes.

INTRODUCTION

Injecting drug users (DU) are at high risk from blood-borne infections, including human immunodeficiency virus (HIV) and hepatitis C virus (HCV), through the sharing of needles and injection equipment [1]. Various approaches to deal with the consequences of hard drugs have been taken; some countries aim to ban illicit drug use completely, whereas the Netherlands and others take a harm reduction approach. This harm reduction approach may have had a major impact on the HIV and HCV epidemic. The ultimate goal of harm reduction is to stop DU from using drugs, but until this is possible the policy is to minimize the damage DU inflict upon themselves and the society at large. Diverse programmes (with a low, medium or high threshold) [2] started in the Netherlands at the
end of the 1970s, providing methadone in combination with social–medical care and needle-exchange facilities. They have no waiting lists and are relatively easy to enter and re-enter. Ongoing drug use during participation is tolerated in low- and medium-threshold programmes. Low-threshold programmes have been operated since 1982 by the Amsterdam Health Service. For clients who have regulated their drug use, methadone can be prescribed in a medium-threshold programme via their general practitioner. Clients who are willing to detoxify can receive methadone in a high-threshold programme through an out-patient addiction clinic. Circulation between the different programmes is permitted and ‘promotion’ to higher-threshold programmes is encouraged.

With the harm reduction approach, the Amsterdam methadone programmes reached an estimated 2700 of the 3500–4000 opiate users in Amsterdam [3]. All services are free of charge for residents of the Netherlands.

The effects of methadone provision or needle exchange programmes (NEP) separately on HIV incidence have been examined, with conflicting results [4,5]. Very few studies describe the effect of either programme on HCV incidence, although declining prevalence of HCV was reported after the introduction of NEP [6].

The Amsterdam Cohort Study (ACS) among drug users comprises a large group of DU who are tested prospectively for HIV. We tested their stored sera for HCV, retrospectively, and therefore had the unique opportunity to document the effect of harm reduction on the incidence of both HIV and HCV over a long time period [7–9].

MATERIALS AND METHODS

Study population and design

The Amsterdam Cohort Study (ACS) among DU 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 infections, as well as the effects of interventions [10]. It has collected detailed information on participation in harm reduction programmes (HRPs). The DU cohort was initiated in 1985; recruitment is ongoing and in recent years has been directed in particular towards young DU.

ACS participation is voluntary, and informed consent is obtained for every participant at intake. ACS participants visit the Amsterdam Health Service every 4–6 months. At intake and every visit, they give blood for HIV testing and storage; they also complete a standardized questionnaire about their health, drug use and sexual risk behaviour and socio-demographic situation. At intake, questions about current behaviour refer to the preceding 6 months and/or to the period since 1980 or since the start of regular use of hard drugs (i.e. heroin, cocaine, amphetamines and/or methadone at least three times per week). At follow-up visits, questions refer to the time between the present and the preceding visit.

Laboratory methods

All ACS participants since 1985 \((n = 1640)\) were tested prospectively for HIV antibodies by enzyme-linked immunosorbent assays (ELISA). All participants with at least two visits between December 1985 and November 2005 \((n = 1276)\) were tested retrospectively 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 (defined as the presence of HCV antibodies in a previously seronegative individual), we tested samples taken between these two visits to indicate the seroconversion interval.

Statistical analyses

HIV- and/or HCV-negative ever-injecting drug users entered the risk set at study entry or at their start of injecting drug use during follow-up, and were followed-up until seroconversion for, respectively, HIV or HCV, or until end of follow up, ultimately at 1 November 2005. The date of HCV or HIV seroconversion was estimated as the midpoint between the last seronegative and the first seropositive ACS visit. Poisson regression was used to determine the effect of harm reduction on HCV and HIV incidence. Incidence rates and incidence rate ratios (IRR) with their corresponding 95% confidence intervals (95% CI) were calculated. We evaluated the potential confounding effect of all variables listed below and evaluated interaction between variables included in the final model. Multivariate models were built using forward-stepwise techniques, and variables with a univariate \(P\)-value \(\leq 0.10\) were considered as potential independent determinants. All variables subject to change were treated as time-dependent variables. A \(P\)-value \(\leq 0.05\) was considered statistically significant.

To study the impact of harm reduction on HIV and HCV seroconversion, we combined injecting drug use, use of NEP and methadone dosage into one variable with five categories (Table 1). Because higher doses of methadone are more effective than lower doses in lowering the prevalence of injecting drug use risk behaviour, we considered \(\geq 60\) mg methadone per day an adequate minimum dosage for opioid replacement therapy and used that dose as cut-off value for our definition of adequate harm reduction [11–13].

General characteristics of persons evaluated included sex, nationality, age, HIV status for HCV as outcome, HCV status for HIV as outcome, HIV status of the steady
partner, homelessness and hospitalization. The drug use variables included current injecting (yes or no), frequency of injecting, main type of drug injected, time elapsed since start of injecting drug use, frequency of non-injecting drug use and type of drug used mainly as non-injecting drug.

**RESULTS**

**General characteristics**

In total, 1640 DU were enrolled in the ACS; 1276 DU had at least two visits. DU with more than one visit were older [median 31.4 (interquartile range (IQR) 31.0–31.8) years versus 28.7 (IQR 28.1–29.4) years], more often male (63.9% versus 56.9%), more often of Dutch nationality (74.5% versus 60.2%) and more often HIV-positive (20.6% versus 16.2%) when compared to DU with only one visit to the ACS.

A total of 952 DU were so-called ever-injecting DU: DU who had ever injected drugs before ACS entry (n = 905) or who started injecting drugs during follow-up (n = 47). Of these ever-injecting DU, 714 were HIV- and/or HCV-negative at study entry and were at risk for HIV and/or HCV during follow-up. One hundred and sixty-four DU (22.9%) were negative for both infections at study entry. 546 DU (76.5%) were HIV-negative and HCV-positive and four DU (0.6%) were HCV-negative and HIV-positive. The HIV prevalence among HCV-negative DU was 2.4% at entry, while the HCV prevalence among HIV-negative DU was much higher (76.2%). The DU included were mainly of Dutch nationality and mainly male (Table 2).

HIV-negative DU had a longer median time since starting injection than HCV-negative DU (respectively, 7.4 and 2.4 years). Furthermore, the proportion of DU who had recently injected (i.e. in the past 6 months before ACS entry) was larger for the HIV-negative DU than for HCV-negative DU. HIV-negative DU injected more often than HCV-negative DU, and HCV-negative DU used non-injecting drugs more often than their HIV-negative counterparts (Table 2). The median follow-up time was 3.56 years (IQR 1.15–7.91 years) for DU at risk for HCV and 8.13 years (IQR 4.25–13.0 years) for DU at risk for HIV.

Under study, 90 of 710 DU at risk for HIV seroconverted and 58 of 168 at risk for HCV. The median duration of the HIV and HCV seroconversion interval between visits was 4.0 months (IQR 3.7–6.0 months) and 4.0 months (IQR 3.7–5.1 months), respectively. The HIV incidence ranged from 8.5 per 100 person-years (PY) in the late 1980s to approximately 0 in the most recent years, whereas HCV incidence was very high in the late 1980s (27.5 per 100 PY) and declined to around two per 100 PY in more recent years [14].

**Effect of harm reduction participation on HIV and HCV incidence**

When evaluating the separate effects on HIV and HCV seroconversion of methadone dose or NEP we found that having any prescribed dose of methadone was associated with lower incidence rates of HIV and HCV infection, but not to a statistically significant degree (P = 0.084 and P = 0.21, respectively). Use of NEP was associated with a higher risk of HIV and HCV seroconversion but, with restriction of this analysis to injecting drugs in the preceding 6 months, the IRR changed towards one and no longer reached statistical significance (data not shown). However, when methadone dose and NEP were combined as described in Table 1, full participation in an HRP was associated with a two- to threefold reduction in the risk of HIV seroconversion and with a six- to sevenfold reduction in the risk of HCV seroconversion (Table 3).
Table 2  General characteristics at entry and during follow-up of 710 HIV-negative and 168 HCV-negative ever-injecting DU included in HIV and HCV analyses, respectively.

|                        | HIV   | HCV   |
|------------------------|-------|-------|
| **At entry**           |       |       |
| HIV/HCV infection (n at risk) | 710 % | 168 % |
| Prevalence HIV infection at entry risk set | – 4 | 2.4 |
| Prevalence HCV infection at entry risk set | 541 76.2 | – |
| Overall HIV incidence (per 100 PY) | 1.65 |       |
| Overall HCV incidence (per 100 PY) |       | 6.78 |
| **General characteristics** |       |       |
| Steady partner at entry | 333 46.9 | 77 45.8 |
| Median age at entry risk set (years; IQR) | 30.0 (27.0–36.0) | 29.0 (25.0–33.0) |
| Female | 274 38.6 | 56 33.3 |
| Dutch nationality | 526 74.1 | 147 87.5 |
| Western European ethnicity | 602 84.8 | 139 82.7 |
| **Injecting drug use** |       |       |
| Median time since start injecting (years; IQR) | 7.21 (3.04–12.1) | 2.43 (0.06–7.16) |
| Injecting in the past 6 months | 524 73.8 | 100 59.5 |
| Among recent injectors injecting more than once a week | 429 82.3 | 53 54.6 |
| Main drug injected |       |       |
| Heroin | 94 17.9 | 33 33.0 |
| Cocaine | 77 14.7 | 14 14.0 |
| Speedball (i.e. combination of heroin and cocaine) | 271 51.7 | 37 37.0 |
| Other | 82 15.6 | 16 16.0 |
| **Non-injecting drug use** |       |       |
| Non-injecting drug use in the past 6 months | 497 70.0 | 149 88.7 |
| Frequency of non-injecting drug use |       |       |
| Once or more times daily | 190 38.2 | 77 51.7 |
| Once or more times weekly, but less than once or more times daily | 188 37.8 | 61 41.0 |
| Less than weekly | 119 23.9 | 11 7.4 |
| Main non-injecting drug use at entry |       |       |
| Heroin | 239 48.2 | 66 44.2 |
| Cocaine | 215 43.3 | 73 49.0 |
| Other | 42 8.5 | 10 6.7 |
| **Follow-up**           |       |       |
| Median number of visits at risk (IQR) | 17 (8–29) | 15 (8–28) |
| Median number of PY (IQR) | 8.13 (4.25–13.0) | 3.56 (1.15–7.91) |
| Median number of days between follow up visits (IQR) | 128 (118–168) | 128 (119–166) |

PY = person years; IQR = interquartile range.
### Table 3: Univariate associations between general characteristics, drug use characteristics, sexual risk behaviour characteristics and HIV and HCV seroconversion among DU in the ACS.

|                      | HIV Incidence (100 PY) | PY | IRR (95% CI) | P-value | HCV Incidence (100 PY) | PY | IRR (95% CI) | P-value |
|----------------------|------------------------|----|--------------|---------|------------------------|----|--------------|---------|
| **Harm reduction**   |                        |    |              |         |                        |    |              |         |
| No harm reduction    | 3.80                   | 18  | 473.6        | 1       | < 0.001                | 23.16 | 11  | 47.5        | 1       | < 0.001 |
| Incomplete harm reduction | 2.80              | 46  | 1640.8       | 0.74    | (0.43–1.27)          | 24.12 | 34  | 141.0       | 1.04    | (0.53–2.05) |
| Full harm reduction  | 1.22                   | 18  | 1475.9       | 0.32    | (0.17–0.62)          | 3.47  | 6   | 173.0       | 0.15    | (0.05–0.40) |
| Limited dependence   | 0.13                   | 1   | 758.1        | 0.035   | (0.005–0.26)         | 0.57  | 1   | 174.9       | 0.024   | (0.003–0.19) |
| No dependence        | 0.57                   | 6   | 1048.4       | 0.15    | (0.060–0.38)         | 1.64  | 5   | 305.2       | 0.071   | (0.025–0.20) |
| **Methadone dosage** |                        |    |              |         |                        |    |              |         |
| 0 mg                 | 2.16                   | 44  | 2036.9       | 1       | 0.084                  | 8.34  | 34  | 407.7       | 1       | 0.21    |
| 0–60 mg              | 1.37                   | 21  | 1531.8       | 0.63    | (0.38–1.07)          | 4.87  | 11  | 226.1       | 0.58    | (0.30–1.15) |
| ≥ 60 mg              | 1.33                   | 25  | 1880.6       | 0.62    | (0.38–1.01)          | 5.67  | 12  | 211.8       | 0.68    | (0.35–1.31) |
| **Needle exchange programme** (% of needles obtained via) | | | | | | | | |
| No recent injecting  | 0.38                   | 10  | 2633.8       | 1       | < 0.001                | 1.60  | 10  | 623.4       | 1       | < 0.001 |
| 0%                   | 3.07                   | 26  | 847.3        | 8.08    | (3.90–16.8)         | 19.66 | 18  | 91.6        | 12.3    | (5.66–26.6) |
| 1–99%                | 2.30                   | 8   | 347.8        | 6.05    | (2.39–15.4)         | 30.56 | 11  | 36.0        | 19.0    | (8.09–44.9) |
| 100%                 | 2.91                   | 46  | 1578.8       | 7.67    | (3.87–15.2)         | 19.10 | 19  | 99.5        | 11.9    | (5.54–25.6) |
| **Change in methadone dosage compared to previous visit** | | | | | | | | |
| No change            | 1.34                   | 39  | 2917.1       | 1       | 0.11                   | 3.73  | 16  | 428.4       | 1       | < 0.001 |
| Increase             | 1.82                   | 18  | 991.5        | 1.36    | (0.78–2.37)          | 3.64  | 5   | 137.2       | 0.98    | (0.36–2.66) |
| Decrease             | 1.67                   | 13  | 778.5        | 1.25    | (0.67–2.34)         | 5.83  | 6   | 102.8       | 1.56    | (0.61–3.99) |
| Unknown              | 2.56                   | 20  | 781.2        | 1.99    | (1.12–3.83)         | 16.51 | 31  | 187.8       | 4.42    | (2.42–8.08) |
| **General characteristics** | | | | | | | | |
| Sex                  |                        |    |              |         |                        |    |              |         |
| Male                 | 1.57                   | 53  | 3384.1       | 1       | 0.62                   | 5.65  | 32  | 566.0       | 1       | 0.085 |
| Female               | 1.78                   | 37  | 2084.3       | 1.13    | (0.74–1.72)         | 8.96  | 26  | 290.2       | 1.58    | (0.94–2.66) |
| Age (per 10 years increase) | 0.52               | 0.69 | (0.39–0.69) | < 0.001 | 0.46                   | 0.46  | 0.65 | (0.32–0.65) | < 0.001 |
| **Homelessness**     |                        |    |              |         |                        |    |              |         |
| No                   | 1.58                   | 82  | 5176.5       | 1       | 0.18                   | 6.5   | 52  | 799.6       | 1       | 0.29   |
| Yes                  | 2.74                   | 8   | 291.9        | 1.71    | (0.83–3.54)         | 10.6  | 6   | 56.7        | 1.63    | (0.70–3.79) |
| **Hospitalization in preceding 6 months** | | | | | | | | |
| No                   | 1.56                   | 80  | 5124.1       | 1.86    | (0.96–3.59)         | 0.09  | 6.85 | 56  | 817.1       | 0.75    | (0.18–3.05) |
| Yes                  | 2.90                   | 10  | 344.3        | 1       | 5.11                   | 5.11  | 2   | 39.2        | 1       | 0.67   |
| **HCV/HIV status at visit** | | | | | | | | |
| Negative             | 1.13                   | 10  | 888.5        | 1       | 0.41                   | 6.13  | 51  | 831.5       | 1       | 0.0055 |
| Positive             | 1.73                   | 79  | 4553.6       | 1.54    | (0.80–2.98)         | 34.82 | 5   | 14.4        | 5.68    | (2.27–14.2) |
| Acute infection in previous 6 months | 4.64               | 1   | 21.6         | 4.12    | (0.53–32.2)         | 19.18 | 2   | 10.4        | 3.12    | (0.76–12.8) |
### Drug use variables

#### Injecting in past 6 months

| Category                     | Yes (n) | 6 months | 6 months | 95% CI | < 0.001 | No (n) | 6 months | 6 months | 95% CI | < 0.001 |
|------------------------------|---------|----------|----------|-------|--------|--------|----------|----------|-------|--------|
| Yes                          | 2.83    | 80       | 2831.1   | 7.45  | (3.86–14.4) | 0.38   | 10       | 2633.8   | 1      |        |        |
| No                           |         |          | 20.74    | 48     | 231.5  | 12.9   | (6.54–25.6) | 0.00   | 10     | 623.4  | 1      |        |

#### Borrowing of needles

| Category                     | Yes (n) | 6 months | 6 months | 95% CI | < 0.001 | No (n) | 6 months | 6 months | 95% CI | < 0.001 |
|------------------------------|---------|----------|----------|-------|--------|--------|----------|----------|-------|--------|
| No recent injecting          | 0.38    | 10       | 2633.8   | 1      |        | < 0.001 | 1.60     | 10       | 623.4  | 1      |
| Recent injecting, no borrowing | 2.71   | 54     | 1996.3   | 7.12  | (3.63–14.0) | 14.51 | 23     | 158.5  | 9.05 | (4.31–19.0) |
| Recent injecting, borrowing 1–9 times | 3.30 | 12 | 363.6 | 8.69 | (3.76–20.1) | 48.11 | 14 | 29.1 | 30.0 | (13.3–67.5) |
| Recent injecting, borrowing ≥ 10 times | 2.17 | 1 | 46.2 | 5.71 | (0.73–4.46) | 23.78 | 2 | 8.41 | 14.8 | (3.25–67.7) |

#### Frequency of injecting drug use in previous 6 months

| Category                     | Yes (n) | 6 months | 6 months | 95% CI | < 0.001 | No (n) | 6 months | 6 months | 95% CI | < 0.001 |
|------------------------------|---------|----------|----------|-------|--------|--------|----------|----------|-------|--------|
| No injecting drug use in previous 6 months | 0.38 | 10 | 2633.8 | 1 | < 0.001 | 1.60 | 10 | 623.4 | 1 | < 0.001 |
| ≥ 2 times/day                | 3.66    | 32       | 874.6    | 9.63  | (4.74–19.6) | 34.72 | 17     | 49.0   | 21.6 | (9.91–47.3) |
| Once/day                     | 2.71    | 3        | 110.6    | 7.15  | (1.97–26.0) | 25.45 | 1      | 3.93   | 15.8 | (2.03–123.8) |
| ≥ 2 times/week               | 3.05    | 29       | 949.6    | 8.04  | (3.92–16.5) | 28.83 | 19     | 65.9   | 18.0 | (8.36–38.7) |
| Once a week                  | 0.00    | 0        | 147.5    | 0     |         | 8.23  | 1      | 12.2   | 5.13 | (0.66–40.1) |
| ≥ 2 times/month              | 2.15    | 5        | 232.1    | 5.67  | (1.94–16.6) | 8.13  | 3      | 36.9   | 5.07 | (1.40–18.4) |
| Once/month                   | 3.92    | 4        | 102.0    | 10.33 | (3.24–33.0) | 15.19 | 2      | 13.2   | 9.47 | (2.07–43.2) |
| Less frequent                | 1.53    | 6        | 393.2    | 4.02  | (1.46–11.1) | 8.36  | 4      | 47.9   | 5.21 | (1.63–16.6) |

#### Main drug injected in previous 6 months

| Category                     | Yes (n) | 6 months | 6 months | 95% CI | < 0.001 | No (n) | 6 months | 6 months | 95% CI | < 0.001 |
|------------------------------|---------|----------|----------|-------|--------|--------|----------|----------|-------|--------|
| No injecting drug use in previous 6 months | 0.38 | 10 | 2633.8 | 1 | < 0.001 | 1.60 | 10 | 623.4 | 1 | < 0.001 |
| Heroin                       | 2.26    | 13       | 574.2    | 5.96  | (2.61–13.6) | 19.62 | 9      | 45.9   | 12.2 | (4.97–30.1) |
| Cocaine                      | 1.81    | 8        | 442.7    | 4.76  | (1.88–12.1) | 24.31 | 10     | 41.1   | 15.2 | (6.31–36.4) |
| Speedball                    | 3.41    | 48       | 1408.6   | 8.97  | (4.54–17.7) | 18.30 | 21     | 114.7  | 11.4 | (5.37–24.2) |
| Amphetamines                 | 1.87    | 4        | 213.9    | 4.92  | (1.54–15.7) | 7.45  |         | 7.45   |     | (1.63–34.0) |
| Methadone                    | 3.02    | 4        | 132.6    | 7.95  | (2.49–25.3) |            |         | 21.3   |     | (5.87–77.5) |
| Other                        | 4.94    | 3        | 60.8     | 13.0  | (3.84–47.2) | 26.92 | 8      | 29.7   | 44.5 | (12.2–161.6) |

#### Time since start injection drug use (years)

| Category                     | Yes (n) | 6 months | 6 months | 95% CI | < 0.001 | No (n) | 6 months | 6 months | 95% CI | < 0.001 |
|------------------------------|---------|----------|----------|-------|--------|--------|----------|----------|-------|--------|
| < 0.93 (0.91–0.96)           | 0.93    | 8        | 42.9     | 13.0  | (3.84–47.2) | 26.92 | 8      | 29.7   | 44.5 | (12.2–161.6) |

### Sexual risk behaviour

#### Heterosexual risk behaviour in previous 6 months

| Category                     | Yes (n) | 6 months | 6 months | 95% CI | < 0.001 | No (n) | 6 months | 6 months | 95% CI | < 0.001 |
|------------------------------|---------|----------|----------|-------|--------|--------|----------|----------|-------|--------|
| No                           | 1.59    | 52       | 3270.9   | 1     |        | 0.87   | 7.57     | 36       | 475.9 | 1      |
| Yes                          | 1.73    | 38       | 2192.5   | 1.09  | (0.72–1.66) | 5.79  | 22      | 380.0  | 0.77 | (0.45–1.30) |

#### HIV status of steady partner

| Category                     | Yes (n) | 6 months | 6 months | 95% CI | < 0.001 | No (n) | 6 months | 6 months | 95% CI | < 0.001 |
|------------------------------|---------|----------|----------|-------|--------|--------|----------|----------|-------|--------|
| No steady partner            | 1.63    | 67       | 4122.5   | 1     |        | 0.0013 | 7.83     | 53       | 676.7 | 1      |
| HIV-positive                 | 6.90    | 10       | 145.0    | 4.24  | (2.18–8.25) | 10.71 | 2      | 18.7   | 1.37 | (0.33–5.61) |
| HIV-negative                 | 1.14    | 11       | 963.7    | 0.70  | (0.37–1.33) | 2.62  | 3      | 114.6  | 0.33 | (0.10–1.07) |
| Unknown HIV status           | 0.98    | 2        | 203.8    | 0.60  | (0.15–2.46) | 0.00  | 0      | 34.0   |     | (0.00–1.00) |

Abbreviations: sc = seroconversion, PY = person years, IRR = incidence rate ratio, 95% CI = 95% confidence interval.
In univariate analysis the following variables were also associated with a higher risk of HIV or HCV: injecting drug use in the past 6 months, borrowing needles in the past 6 months, more recent onset of injecting drug use, a higher frequency of injecting drugs, mainly injecting speedball, younger age and having an HIV-positive steady partner. A change in methadone dosage in the past 6 months was associated with a higher risk for HCV seroconversion but not HIV seroconversion. DU who were chronically HIV-infected or had an acute HIV infection in the 6 months preceding the visit were at increased risk for HCV seroconversion (Table 3).

In multivariate analysis we found that after correcting for having an HIV-positive steady partner and a smaller number of years since starting injection (both factors being associated independently with HIV seroconversion), the combined harm reduction variable remained associated independently with HIV seroconversion (Table 4). That is, DU fully participating in HRPs were at a decreased risk of HIV seroconversion compared to DU not participating fully in an HRP (IRR 0.43, 95% CI 0.21–0.87).

In multivariate analysis for HCV, we found that with correction for time elapsed since start of injection, DU participating fully in an HRP were at decreased risk of HCV seroconversion compared to DU not participating in an HRP (IRR 0.36, 95% CI 0.13–1.03). As with HIV, DU who recently started injecting drug use were at increased risk of HCV seroconversion. The effect of HIV status of the steady partner on HCV incidence had the same direction as its effect on HIV incidence (Table 4).

In sensitivity analyses, we found that the effects of harm reduction on HIV and HCV seroconversion did not change substantially when analysis was restricted to the years after 1989 (i.e. when a methadone dose of ≥ 60 mg daily was more readily available for DU). Also, when the lower limit of adequate methadone dosage was adjusted to ≥ 80 mg daily, the effects of harm reduction on HIV and HCV seroconversion did not change substantially.

**DISCUSSION**

Our data suggest that the combination of adequate methadone therapy and full participation in NEP contributed substantially to the reduction of the incidence of HIV and HCV in DU in Amsterdam, although a statistically significant effect was not seen when methadone dose or NEP were considered separately. It is likely that Amsterdam’s comprehensive programme, in which methadone treatment and NEP are combined, explains the reported decline of HIV and HCV incidence.

We found no evidence that the effect of harm reduction was larger on HCV incidence than on HIV incidence, as our risk estimates for the different levels of harm reduction participation were comparable. One explanation might be that the Amsterdam harm reduction approach, which maintains contact with as many DU as possible, has an effect not only on injecting but also on sexual risk behaviour due to counselling and condom distribution. Our findings are in line with the reduction of sexual and drug-related risk behaviour seen in the ACS since the mid-1990s [7]. Having an HIV-positive steady partner was associated with a higher risk of HIV infection, showing that HIV is sexually transmitted more effectively than HCV.

The evaluation of HRPs is complicated because it is difficult to link participation in HRPs to outcome vari-

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**Table 4** Multivariate analysis of the effect of participation in harm reduction programmes on HIV and HCV seroconversion.

|               | HIV                  |          | HCV                  |          |
|---------------|----------------------|----------|----------------------|----------|
|               | IRR  | 95% CI      | P-value | IRR  | 95% CI      | P-value |
| Level of harm reduction (definitions described in Table 1) |       |           |          |       |           |          |
| No harm reduction | 1   | < 0.001    |          | 1     | < 0.001    |          |
| Incomplete harm reduction | 0.87 | 0.50–1.52  |          | 1.17  | 0.59–2.31  |          |
| Full harm reduction | 0.43 | 0.21–0.87  |          | 0.36  | 0.13–1.03  |          |
| Limited dependence on harm reduction | 0.046 | 0.006–0.35 |          | 0.044 | 0.006–0.35 |          |
| No dependence on harm reduction | 0.20 | 0.078–0.50 |          | 0.13  | 0.044–0.40 |          |
| Time since start injection drug use (per year) | 0.95 | 0.92–0.98  | < 0.001 | 0.87  | 0.81–0.93  | < 0.001 |
| HIV status of steady partner |       |           |          |       |           |          |
| No steady partner | 1   |          | 0.004   | 1     |          | 0.026   |
| HIV-positive steady partner | 4.53 | 2.23–9.21 |          | 3.49  | 0.84–14.5 |          |
| HIV-negative steady partner | 0.82 | 0.43–1.57 |          | 0.42  | 0.13–1.37 |          |
| Steady partner with unknown HIV status | 0.75 | 0.18–3.06 |          |       |           |          |

IRR = incidence rate ratio, 95% CI = 95% confidence interval.
Effective harm reduction on HIV and HCV incidence

Our finding is most important for countries with recent and sometimes explosive outbreaks of HIV and/or HCV among DU, as in the former Soviet Union and Asia [22,23]. To provide needles and syringes only or methadone only will not be sufficient to curb the rapid spread of these and other blood-borne infections among DU. It is essential to offer a comprehensive programme in which both measures are combined, preferably also with social–medical care and counselling.

Acknowledgements

The authors would like to thank J. Bax and A. Snuverink for data collection and blood sampling; all subjects for their participation; the Departments of Human Retrovirology and Clinical Virology of the Academic Medical Center in Amsterdam, the Netherlands, for HIV and HCV testing; Dr R. Geskus for his contribution to the manuscript; and L. Phillips for the editing of the manuscript. Financial support: the 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 supported financially by the Netherlands National Institute for Public Health and the Environment (available at: http://www.amsterdamcohortstudies.org).

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