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Title page

The effect of needle and syringe program and opioid agonist therapy on the risk of HIV, hepatitis B and C virus infection for people who inject drugs in Amsterdam, the Netherlands: findings from an emulated target trial

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Background and aims: Major declines in HIV and hepatitis C and B virus (HCV / HBV) incidence among people who inject drugs (PWID) have been attributed to early implementation of harm-reduction programs (HRP) in the Netherlands; but alternative factors such as selective mortality and demographic and drug markets shifts over time likely contributed to observed incidence declines. We quantified and tested the effect of HRP participation on risk of these infections among PWID in Amsterdam, the Netherlands.

Design: We emulated the design of a hypothetical, ideal randomized trial using observational data from the Amsterdam Cohort Studies (1985-2014).

Setting: Amsterdam, the Netherlands

Participants: We included PWID who ever used opioids, had a recent history of injecting drug use (IDU) and tested negative for HIV, HCV, or HBV.

Interventions: Intervention arms were: complete HRP participation (≥60 mg/day methadone and 100% needle and syringe program (NSP) coverage, or any methadone dose if no recent injection drug use) versus no HRP and partial HRP participation combined (<60 methadone mg/day and/or <100% NSP coverage).

Measurements: Separately for each infection, we estimated the hazard ratios (HR) comparing HRP arms using marginal structural models.

Findings: Of 983 participants, 640, 137 and 308 were included for the HIV, HCV and HBV analyses and 59, 45 and 49 seroconversions were observed, respectively. Compared to no/partial HRP participation, complete HRP participation led to lower risk of HIV (HR=0.54, 95%CI:0.27-1.08), HCV (HR=0.16, 95%CI:0.06-0.40) and HBV (HR=0.28, 95%CI:0.13-0.61) acquisition.

Conclusions: Complete participation in HRP led to substantial decreases in HIV, HCV and HBV acquisition risk among PWID in the Netherlands. Findings reinforce the need to implement or scale-up complete and combined HRP to prevent transmission of these infections.

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Introduction

People who inject drugs (PWID) are a key population at risk of HIV, hepatitis C virus (HCV) and hepatitis B virus (HBV) acquisition through sharing of contaminated needles/syringes and other injecting equipment [1]. In many countries, injection drug use is the leading exposure for ongoing transmission for these infections. However, in the Netherlands it currently does not play a substantial role in the transmission of HIV and other blood-borne infections and incidence has remained nearly zero over the last two decades [2, 3].

Several factors have been proposed to explain the decline in incidence of these infections among PWID. First, the Netherlands was one of the first countries to provide low-threshold opioid agonist therapy (OAT) in the 1970s [4], and from 1991 onwards policy changed to provide higher doses of methadone (≥60mg/day) [5]. In 1984, it became the first country in the world to implement a needle and syringe program (NSP) [6]. Individual and meta-analysis studies have reported that harm reduction programs (HRP), particularly the combination of OAT and NSP, are associated with a decreased risk of HIV and HCV acquisition [7, 8]. Second, high mortality from HIV among PWID in the Netherlands during the early 1990s may have led to a decline in prevalence of HIV and HCV, reducing the risk of exposure among susceptible PWID [9]. Third, in conjunction with the decline in incidence, injecting drug use (IDU) declined among lifetime PWID and there was a decrease in new initiates to injection drug use [6, 9]. Importantly, this decline in IDU among lifetime PWID may also have been attributable to the high coverage of low-threshold HRP, including OAT. However, it remains unknown to what extent HRP was able to curb the HIV and HCV epidemics among PWID in The Netherlands.

While the association of HRP with HIV and HCV acquisition has been reported [7, 8], the evidence has been obtained from observational longitudinal studies, with insufficient adjustment for confounding and selection bias. A Cochrane review on the association of HRP participation and HCV incidence indicated that based on risk of bias assessment, most of the included studies were at serious or critical risk of bias and provided weak or very weak evidence [7]. In addition, time-varying confounding (i.e. frequency of injecting drug use) can be affected by previous treatment (i.e. HRP participation), inducing a bias known as treatment-confounder feedback [10]. Therefore traditional statistical methods are likely to provide biased estimates [10]. A randomized-control trial would provide the strongest evidence possible for a causal effect of HRP on acquisition of these infections. However, as the benefits of HRP in improving health outcomes of PWID are widely recognized, it would be unethical to include an arm without HRP [11, 12]. Novel methods for causal inference have been proposed to address statistical issues in traditional statistical methods utilizing observational data [10]. Using observational data from

PWID participating in the Amsterdam Cohort Studies (ACS), we aimed to estimate the effect of combination NSP and OAT on HIV, HCV and HBV infection risk.

Methods

Cohort population

We used data from PWID participating in the ACS between 1985-2014. In summary, the ACS was a prospective observational cohort study that began in 1985 and remained open until 2014 [13]. Participants were recruited at methadone outposts, a sexually transmitted infection outpatient clinic for sex workers who used drugs (until 1997), and by word of mouth. Participants made follow-up visits every 4 months until 2003 and thereafter every 6 months. At each visit, participants were interviewed by trained research nurses about their health and sexual and drug-use behaviour using a standardized questionnaire. For participants who did not return for follow-up, information about vital status was obtained annually by matching against local population registries. The study was approved by the Medical Ethical Committee of the Amsterdam Medical Centre, the Netherlands. The present research question and hypothesis were included in the Aidsfonds grant application to support this work prior to commencement of this project (project number 29703).

Target trial emulation

Using data from the ACS, we emulated the study design and statistical analyses of a target trial [14] by using each of the following protocol components: eligibility criteria, intervention strategies, outcome definition, follow-up, causal contrasts and statistical analyses. Supplementary Table 1 describes in detail each protocol component and their emulation using ACS data. We report study procedures and results in accordance with STROBE guidelines (Supplementary Materials).

Eligibility criteria

Individuals were eligible if they had ever reported using opioids (including methadone) and had at least one IDU episode in the two-year period prior to the start of follow-up of the analysis. Individuals also had to be at risk for HIV, HCV and/or HBV acquisition based on a negative HIV, HCV and hepatitis B core (anti-HBc) antibody result, respectively, for the pertaining infection analysis (Testing procedures can be found in the supplement).

Intervention strategies

We considered two HRP interventions based on self-reported level of NSP coverage and current IDU since the previous cohort visit or last 6 months prior to cohort enrolment, and current daily prescribed methadone dosing (Supplementary Table 2):

1. No/Partial HRP defined as no participation in HRP or suboptimal utilization of HRP (defined as <100% NSP coverage and/or a methadone dose of <60 mg/day) among PWID reporting current IDU.
2. Complete HRP defined as 100% coverage of NSP and ≥60 mg/day methadone among PWID reporting current IDU. Among PWID who did not report IDU since the previous visit, any dose of methadone was considered complete HRP participation.

Outcome

The outcomes of interest, which were analysed separately, were HIV, HCV and HBV seroconversion. The date of seroconversion was estimated as the midpoint date between the first positive test date and last negative test date.

Follow-up

Each individual was followed-up from the visit they met all the eligibility criteria (baseline) until incident infection, the visit they stopped being adherent with their baseline harm reduction strategy (i.e., switched intervention strategies during follow up), loss to follow-up (i.e., not seen for more than two years), administrative censoring date or two years after baseline, whichever occurred first. The administrative censoring date was 31 December 2014 for analysis on HIV and HCV and 31 December 2002 for HBV. The data were structured such that cohort visits occurred every four to six months after the baseline cohort visit.

Casual contrast

Our analysis estimates the effect of participating in complete HRP participation versus no/partial participation continuously for two years after baseline. We therefore estimate the target trial analogue of a per-protocol effect.

Statistical analyses

PWID were classified as participating in complete versus no/partial HRP based on the information on HRP participation at the baseline visit when the eligibility criteria were met, and complete data were available. Follow-up was censored from the visit at which the participant deviated from their initial baseline HRP participation status (i.e., non-adherence). Since participation in HRP was highly variable within PWIDs over time (Figure 1), participants could meet the inclusion criteria multiple times. Therefore, we designed the study to emulate a sequence of trials starting each year between 1985 and 2014, with a maximum duration of two years for each 'trial'. This approach allows individuals to be

included multiple times as long as they meet the eligibility criteria and is more statistically efficient than choosing the first or a random eligibility episode as time zero [15]. All 'trials' were pooled into a single analysis. Stopping both injecting and OAT use was considered as remaining adherent, regardless of intervention. For the time-varying confounders the last observations were carried forward until a new measurement became available or two years after the most recent visit.

We used marginal structural models to estimate the effect of complete versus no/partial HRP participation on HIV, HCV and HBV incidence. Under the untestable assumptions of unmeasured confounding, correct model specification and positivity the effect estimate can be interpreted as a causal effect [10]. In the first step, we computed time-varying nonstabilized weights defined as the inverse of the probability of complying with the baseline HRP participation status. More specifically, we fitted a pooled logistic regression model including the HRP participation status (i.e., complete vs no/partial) as outcome, adjusting for baseline and time-varying confounders and time since baseline. To account for informative loss to follow-up, we calculated inverse probability of censoring weights using a logistic regression model adjusting for all confounders, HRP participation status and time since baseline. The final weights were calculated by multiplying the treatment and censoring inverse probability weights (IPWs) and were truncated at a maximum of 10. Finally, we fitted a pooled logistic regression models including the final weights to estimate the hazard ratio (HR) of the outcomes for complete versus no/partial HRP participation. To account for repeated participation in multiple trials per individual, we calculated 95% confidence intervals (95%CI) using the 2.5%tile and 97.5%tile from bootstrapped variance estimations of 1000 samples with replacement.

Confounders were selected based on peer-reviewed literature and expert opinion [16-20], as illustrated in Figure 2. Baseline confounders were time since first IDU, age at IDU initiation and gender. Time-varying confounders were frequency of IDU (daily, weekly and monthly/no IDU) and having a current/lifetime PWID steady sexual partner. More details on the confounder selection can be found in the supplementary material.

We carried out analyses using Stata (v15, College Station, TX).

Sensitivity analyses

As the effect of HRP participation might differ in those who currently inject, we restricted all analyses where only current PWID were eligible to participate. Second, as HRP and frequency of IDU were measured at the same visit, the temporal order when these events took place is unknown. Therefore,

we performed another sensitivity analysis using data from the self-reported frequency of IDU from the prior visit (i.e., lagged frequency of IDU). For comparison purposes, we also performed unweighted and intention-to-treat (ITT) analyses for each infection using the same target trial approach as well as analysis using stabilized weights. Lastly, we performed an E-value analysis to assess the minimum strength of association that "unstable housing" (a potential unmeasured confounder) would need to have with both HRP participation and infection risk to explain away the observed effect estimates [21, 22] (Details of the Intention-to-treat and E-value analysis in the supplement).

Results

Of 1,661 people who used drugs participating in the ACS, 1,303 had at least two follow-up visits between 1985 and 2014 (Figure 3). We further excluded 320 participants who reported never injecting drugs. After removing people who tested positive at cohort enrolment, 640, 137 and 308 PWID were included for the HIV, HCV, and HBV analyses, respectively, and 59, 45 and 49 seroconversions were observed within the pooled at-risk follow up (Figure 3). Among PWID considered eligible for analysis at least once, incidence of HIV, HCV and HBV significantly declined over calendar years: from 3.3 (95% confidence interval (CI):1.6-7.0), 39.0 (95%CI:11.3-80.3), 8.5 (95%CI: 1.7-11.8) per 100 person-years (PY) in 1989, to 0.3 (95%CI: 0.05-2.4), 5.0 (95%CI: 1.3-20.1) and 1.0 (95%CI: 0.1-7.5) per 100 PY in 1999, respectively and zero in 2010 for HIV and HCV (Supplementary Figure 1). When only current PWID at baseline were included, 614, 123 and 293 were eligible for the HIV, HCV and HBV analyses and 63, 48 and 50 seroconversions were observed, respectively.

The median number of 'trial' participations and median duration between visits, respectively, were: 2 (IQR:1-3) and 0.4 years (IQR: 0.3-0.5) for the HIV analysis, 1 (IQR:1-2) and 0.4 years (IQR: 0.3-0.5) for HCV and 1 (IQR:1-2) and 0.3 years (IQR: 0.3-0.4) for HBV, respectively. The distribution of socio-demographic and behavioural characteristics for the visit at which PWID were first considered eligible are shown in Table 1, and by intervention and infection risk in Supplementary Tables 5, 6 and 7. Throughout follow-up, visits at which participants who injected drugs reported heroin use ranged between 95-97% for all three infections, often in combination with injecting cocaine (i.e., speedball). The proportion of individuals who participated in complete HRP increased over calendar time (Figure 1B).

HIV infection

Complete HRP participation led to a 45% decrease in risk of HIV acquisition (HR=0.54, 95%CI:0.27-1.08), p-value=0.081) compared to no/partial HRP participation (Figure 4 & Supplementary Table 4). The mean IPWs were 5.3 (standard deviation (SD)=3.4) (Supplementary Figure 3). In the subset of 614 current PWID at baseline, there was a 32% decreased risk of HIV acquisition (HR=0.68, 95%CI=0.35-1.34, p-value=0.267, mean IPWs =4.0 (SD=3·0), Supplementary Figure 4).

HCV infection

Complete HRP participation led to an 84% decrease in risk of HCV acquisition (HR=0.16, 95%CI:0.06-0.40, p-value<0.001; mean IPWs=5.7 (SD=3.5)) compared to no/partial HRP participation (Figure 4, Supplement: Table 4 & Figure 3). In the subset of 123 current PWID at baseline, there was a 76%

decreased risk of HCV acquisition (HR=0.24, 95%CI=0.08-074, p-value=0.013, mean IPWs=3.2 (SD=2.8), Supplementary Figure 4).

HBV infection

Complete HRP participation led to a 72% decrease in risk of HBV acquisition (HR=0.28, 95%CI:0.13-0.61, p-value=0.001; mean IWPs=5.5 (SD=3.5)) compared to no/partial HRP participation (Figure 4, Supplement: Table 4 & Figure 3). In the subset of 293 current PWID at baseline, there was a 63% decrease risk of HBV acquisition (HR=0·37, 95%CI=0.13-1.05, p-value=0.062, mean IPWs=3.7 (SD=2.9), Supplementary Figure 4).

The sensitivity analysis using lagged frequency of IDU and stabilized weights led to similar results as the main analysis. Standard unweighted Cox-models and the ITT analyses resulted in HRs closer to the null compared to the per-protocol weighted models for all three infections (Supplement: Table 4 & Figure 2).

Discussion

Using data from a long-standing prospective observational study of PWID, we estimated the effect of HRP participation on infection risk in an emulated trial: compared to no or partial participation, complete HRP participation led to a reduction in infection acquisition of 45% for HIV, 84% for HCV and 72% for HBV.

A previous modelling study suggested that in some scenarios the decline in HIV and HCV incidence among PWID in the Netherlands was consistent with demographic changes in the PWID population, though the best fitting model assumed a strong decrease in risk behaviour as a result of HRP [9]. Additionally, this study also reported that high-risk PWID acquiring HIV early in the epidemic and having high mortality from HIV resulted in a reduction in the pool of high-risk PWID [9]. Our current finding of a strong protective effect of HRP on infection risk and its increased uptake over calendar time in Amsterdam suggests that HRP has averted new HIV and Hepatitis C and B infections in Amsterdam.

Prior to our study, little was known regarding the effect of HRP on HBV acquisition. A systematic review reported findings from two observational studies with HBV infection as the outcome found either a decreased risk of HBV acquisition or no association. Our findings support a strong effect of complete HRP participation on HBV acquisition. As HBV immunisation coverage remains suboptimal for PWIDs in many settings [23, 24], our study suggests that complete HRP participation should be considered an important component of any HBV elimination strategy. Given that HBV is the only one of these three infections for which we have a vaccination, HBV immunisation should be included in HRP for PWID.

The reasons complete HRP participation led to reductions in HIV, HBV and HCV infection among PWID in the Netherlands are likely multifold. First, by using sterile injecting equipment (including needles and syringes) at every injecting occasion the mode of transmission is interrupted. Second, OAT is associated with decreased frequency of injecting and with short- and long-term injection cessation [8]. Given that injection cessation is likely a direct result of HRP participation, it would mediate the effect of HRP on infection risk. Moreover, participation in HRP forms a point-of-contact with health care services that provide care beyond HRP such as referral to health and welfare services and sexual health counselling including the provision of condoms, likely contributing to decreased injecting frequency and infection risk. One important finding was that complete HRP had greater impact on HCV acquisition than on HIV and HBV. This could be explained by the fact that HIV and HBV are more likely to be transmitted via sexual contact than HCV [25] and a higher prevalence of HCV among PWID.

In the Netherlands, drug consumption rooms, available since 1994 [26], and heroin co-prescription with methadone, available since 1998 as part of a randomized study and registered in 2009 as a treatment [27] may have also contributed to decreased transmission of these infections. Heroin co-prescription has been shown to reduce 'street' use of heroin which may help PWID avoid unsafe injecting practices [28]. Drug consumptions rooms are associated with reductions in syringe sharing, although evidence from longitudinal studies is scarce [29]. In our analyses, some individuals assigned to the no/partial HRP arm may have received heroin co-prescription and thus could be viewed as participating in complete HRP. However, as most of included data was from the early 1990s and very few PWID included in our study population reported heroin co-prescription after 2009 (0-1%, data not shown), bias from heroin co-prescription would be unlikely.

Due to self-selection of HRP participation among individuals at high risk of infection acquisition, any adjustment for confounding using standard regression would typically lead to HRs closer to one. Accordingly, in the unweighted models we observed estimates of HRP closer to the null on all infections. When considering a meta-analysis from three studies using standard methods with high risk of bias (including a previous study from the ACS [7]), a pooled adjusted reduction in HCV acquisition of 74% was observed. In our study, the reduced risk was 84%, suggesting a slightly stronger protective effect. The studies included in the meta-analysis insufficiently corrected for allocation to exposure arms, did not correct for biases induced by loss to follow-up, and inappropriate methods for time-varying confounding were used. Our approach aims to address these limitations by using inverse probability weighting to adjust for time-varying confounding [10] and emulating the design of an ideal hypothetical trial to decrease the risk of selection bias [30]. We attempted to do so by aligning the components of an ideal randomized control trial (e.g., eligibility, follow up) to our observational data.

We also observed a stronger beneficial effect of HRP in our main analysis compared to analyses where only current PWID at baseline were eligible for the study. As former/non-active PWID receiving OAT were included in the complete arm in the main analysis, this group is less susceptible to infection acquisition and hence the effect of complete HRP is probably accentuated. More importantly, the protective effect of HRP remained when including only current PWID at baseline. This finding coupled with the fact that long-term drug use cessation is uncommon (abstinence: 28% at 20 years since regular drug use initiation in the ACS [31]), highlights that HRP participation is crucial in reducing infection acquisition irrespective of whether PWID are actively injecting drugs.

Limitations

Our study has limitations. We did not have complete data on unstable housing throughout follow-up which is known to be associated with injection frequency and infection acquisition [32]. In our study, we assumed that unstable housing would only affect infection acquisition through frequency of injecting and HRP participation. If this assumption is correct, adjusting for unstable housing would be unnecessary. Based on the E-value analyses, the association between unstable housing and both HRP participation and infection risk would need to be very strong to explain away the current effect estimates, particularly for HCV and HBV [21]. Also, although the protective association of HRP among females has been reported to be weaker than among males [7], we could not include an interaction term between HRP and sex due to lack of power. Moreover, although most participants were primarily injecting heroin, for some PWID, OAT may not have been indicated, potentially underestimating the effect of complete HRP. In addition, we assume that HRP participation prior to baseline does not have a significant impact on infection risk, and we estimate the effect of current HRP participation. As we do not have HRP participation history data prior to ACS enrolment, we are not able to check this assumption. Lastly, as participation in HRP was high and very few individuals reported no HRP use, we could not independently evaluate 'no HRP use' as a comparator strategy. In our study, the no/partial HRP participation arm is more reflective of partial HRP participation. Nevertheless, we found strong evidence on the effect of complete HRP in reducing HIV and hepatitis C and B, which suggests that the simultaneous provision of both services is required to reduce the number of new infections.

There is also question of the respective relative contributions of NSP and OAT to the reduction of infection incidence. Associations between NSP or OAT alone and HIV and HCV infection acquisition are variable, and studies have shown stronger protective effects on HIV and HCV where PWID have optimal combination of NSP and OAT rather than each HRP component alone or with suboptimal use [3, 33]. In our emulated trial, we investigated exposure to complete or high coverage HRP participation rather than seeking to disentangle each HRP component or to assess the impact of moderate levels of HRP versus no HRP. This would be difficult to assess among PWID participating in the ACS given the almost universal exposure to some HRP, multiple transitions participants made over the follow-up period, and the fact that most participants tended to use both HRP components concurrently, but may be possible in other studies.

Coverage of HRP remains low in many countries with a high burden of IDU and blood-borne infections among PWID [34]. Importantly, even in countries with a declining incidence of these infections, scaling down the coverage or intensity of these services can lead to sudden increases in HIV incidence [35]. This was observed in Athens where the 2008 economic crisis preceded an HIV outbreak among PWID

[36]. Moreover, in the last decade several rural counties in the US with low coverage of HRP have reported outbreaks of HIV and HCV fuelled by the opioid crisis [37]; and in Glasgow HIV outbreak HRP services failed to respond to changing drug use patterns [38]. Scaling up HRP could prove beneficial. As we strive to eliminate HIV and viral hepatitis in the coming decade, HRP will likely play a crucial role in reducing infection acquisition, including HCV reinfection, in PWID and can provide points-of-care for testing and treatment, as well as supporting treatment adherence [39]. For instance, a modelling study of 11 European cities or countries projected that scaling-up NSP and OAT coverage to 80% would reduce the need to scale-up HCV treatment with direct-acting antivirals by 20-80% while still reducing incidence below 2% by 2026 [40]. In the US, HCV elimination targets are unlike to be met without scaling up HRP [41].

Conclusions

We found that complete participation in both NSP and OAT led to a major decrease in risk of HIV, HCV and HBV acquisition among PWID in the Amsterdam Cohort Studies between 1985 and 2014. These findings reinforce the need to implement, scale up and facilitate high coverage HRP participation to prevent ongoing transmission of these infections among PWID.

Table 1: Baseline socio-demographic and behavioral characteristics and follow-up data of PWID participating in the Amsterdam Cohort Studies by infection risk (1985-2014)

Characteristic	HIV (N=640)	HCV (N=137)	HBV (N=308)
Age at start IDU (years)			
Median (IQR)	22.3 (18.0, 27.1)	25.3 (21.1, 30.9)	23.3 (19.4, 28.3)
Sex			
Male	403 (63.0%)	93 (67.9%)	199 (64.6%)
Female	237 (37.0%)	44 (32.1%)	109 (35.4%)
Baseline year			
Median (IQR)	1991 (1987, 1996)	1994 (1989, 1999)	1992 (1988, 1995)
Time since first IDU			
Median (IQR)	6.8 (2.4, 12.9)	0.9 (0.0, 6.0)	4.6 (1.0, 9.0)
Frequency of IDU since last visit			
No IDU	58 (9.1%)	26 (19.0%)	34 (11.1%)
Monthly	225 (35.3%)	24 (17.5%)	83 (27.0%)
Weekly	239 (37.5%)	34 (24.8%)	108 (35.2%)
Daily	116 (18.2%)	53 (38.7%)	82 (26.7%)
Drug most frequently injected since last visit[1,2]			
Heroin	122 (21.0%)	36 (32.4%)	66 (24.1%)
Cocaine	77 (13.2%)	13 (11.7%)	46 (16.8%)
Heroin and Cocaine	305 (52.4%)	45 (40.5%)	132 (48.2%)
Amphetamine	33 (5.7%)	9 (8.1%)	10 (3.6%)
Methadone	8 (1.4%)	4 (3.6%)	4 (1.5%)
Other	37 (6.4%)	4 (3.6%)	16 (5.8%)
Non-IDU drug most frequently used since last visit[3]			
Heroin	116 (36.6%)	35 (34.7%)	72 (41.9%)
Cocaine	66 (20.8%)	17 (16.8%)	26 (15.1%)
Heroin and Cocaine	104 (32.8%)	42 (41.6%)	63 (36.6%)

Characteristic	HIV (N=640)	HCV (N=137)	HBV (N=308)
Amphetamine	25 (7.9%)	4 (4.0%)	8 (4.7%)
Other	6 (1.9%)	3 (3.0%)	3 (1.7%)
Steady PWID partner since last visit			
No partner or never PWID	479 (74.8%)	109 (79.6%)	233 (75.6%)
Yes, ever or current PWID	161 (25.2%)	28 (20.4%)	75 (24.4%)
HIV status of steady partner since last visit			
No partner or unknown status	537 (84.0%)	114 (83.2%)	253 (82.1%)
HIV negative	18 (2.8%)	4 (2.9%)	8 (2.6%)
HIV positive	65 (10.2%)	12 (8.8%)	34 (11.0%)
HIV unknown	19 (3.0%)	7 (5.1%)	13 (4.2%)
Type of steady sexual partner			
No steady partner	383 (59.9%)	92 (67.6%)	187 (60.7%)
Same sex (male)	11 (1.7%)	3 (2.2%)	8 (2.6%)
Heterosexual	244 (38.2%)	41 (30.1%)	112 (36.4%)
Same sex (female)	1 (0.2%)	0 (0.0%)	1 (0.3%)
Ever engaged in sex work since last visit			
No	341 (53.3%)	74 (54.0%)	172 (55.8%)
Yes	299 (46.7%)	63 (46.0%)	136 (44.2%)
Current methadone dosing in mg/day			
0	138 (21.6%)	47 (34.3%)	82 (26.6%)
1 - 59	347 (54.2%)	56 (40.9%)	152 (49.4%)
≥60	155 (24.2%)	34 (24.8%)	74 (24.0%)
Needle and syringe program coverage since last visit			
0%	287 (45.8%)	82 (63.1%)	158 (52.1%)
1 - 99%	96 (15.3%)	12 (9.2%)	33 (10.9%)
100%	244 (38.9%)	36 (27.7%)	112 (37.0%)

Characteristic	HIV (N=640)	HCV (N=137)	HBV (N=308)
Baseline harm reduction intervention arms			
No/Partial HRP	517 (80.8%)	103 (75.2%)	245 (79.5%)
Complete HRP	123 (19.2%)	34 (24.8%)	63 (20.5%)
Person years of follow up[4]			
Median (IQR)	2.6 (1.0, 7.6)	1.3 (0.0, 2.6)	1.8 (1.0, 4.0)
Number of seroconversions during follow up			
Events	59	45	49

Abbreviations: HCV: Hepatitis C virus; HBV: Hepatitis B virus; IDU: Injection drug use; HRP: Harm reduction program; IQR: interquartile range. Missing values excluded.

[1]Among PWID reporting current IDU.

[2]The category *mainly methadone* was included from 1989 onwards. Heroin/cocaine category includes both simultaneous use (i.e., speedball) and when the same frequency of drug use was reported for both heroin and cocaine.

[3]Frequency of use based on reported heroin, cocaine, and amphetamines non-IDU use. Barbiturates/tranquilizers were excluded as it unknown whether these were used as prescribed medication or for recreational drug use.

[4]Time between first and last cohort visit date included in the analyses.

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Declaration of interest:

None of the other authors had any conflict to declare related to this study.

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