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Decline in incidence of HIV and hepatitis C virus infection among injecting drug users in Amsterdam; evidence for harm reduction?

Anneke S. de Vos[1], Jannie J. van der Helm[2], Amy Matser[1,2], Maria Prins[2,3] & Mirjam E. E. Kretzschmar[1,4]

Julius Center, University Medical Center Utrecht, Utrecht, the Netherlands,[1] Cluster Infectious Diseases, Public Health Service Amsterdam, Amsterdam, the Netherlands,[2] Department of Internal Medicine, CINIMA, Academic Medical Center, Amsterdam, the Netherlands[3] and Centre for Infectious Disease Control, RIVM, Bilthoven, the Netherlands[4]

ABSTRACT

Aims In Amsterdam, HIV prevalence has nearly halved among injecting drug users (IDU) since 1990. Hepatitis C virus (HCV) prevalence also declined; HIV and HCV incidence dropped to nearly zero. We examined possible explanations for these time trends, among which the implementation of harm reduction measures aimed at reducing the risk behaviour of IDU. **Design** We used individual-based modelling of the spread of HIV and HCV. Information about demographic parameters was obtained from the Amsterdam Cohort Study (ACS) among drug users. The model included changes in inflow of new IDU and death rates over time, the latter dependent on age and time since HIV seroconversion. We considered different scenarios of risk behaviour. **Setting** IDU in Amsterdam. **Measurements** Simulated HIV and HCV incidence and prevalence were compared with ACS data. **Findings** Assuming that harm reduction measures had led to a strong decrease in risk behaviour over time improved the model fit (squared residuals decreased by 30%). However, substantial incidence and HIV prevalence decline were already reproduced by incorporating demographic changes into the model. In particular, lowered disease spread might be a result of depletion of high-risk IDU among those at risk for disease, and a decrease in the number of high-risk individuals in the population due to HIV-related mortality. **Conclusions** Marked decreases in HIV and HCV in Amsterdam since 1990 could be due partly to harm reduction measures; however, they may also be attributable largely to changes in the IDU population. Future research aimed at quantifying the benefits of interventions should not neglect the impact of natural epidemic progression and demographic changes.

Keywords Demography, harm reduction, HCV, HIV, injecting drug use, theoretical models.

Correspondence to: Anneke S. de Vos, Julius Center, University Medical Center Utrecht, stratenum 6.131, postbus 85500, Utrecht 3508GA, Netherlands.
E-mail: A.S.deVos-4@umcutrecht.nl
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INTRODUCTION

Harm reduction is a general term used for interventions aimed at minimizing harm from drug use to society at large and to drug users themselves [1]. Through sharing of used syringes and other injecting equipment, blood-borne infections such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV) are spread among injecting drug users (IDU). Efforts that could limit the spread of these viruses include needle exchange programmes, opiate substitution (mainly methadone prescription) therapy and risk education programmes.

Although there is evidence that harm reduction can be effective, in particular for lowering HIV incidence (which is transmitted less easily through blood–blood contact than HCV), there is still ongoing discussion as to whether the evidence is conclusive [2–5]. The studies on which the arguments for harm reduction are based are mainly observational studies, which may be severely biased by demographic processes and intrinsic dynamics of disease epidemics [6–8]. Although these confounders can be taken into account using mathematical models, studies explicitly addressing their impact are rare [9].

In Amsterdam, harm reduction interventions have been implemented since the rise of HIV in the 1980s [10].

Needle exchange began in the mid-1980s and has been at full capacity since approximately 1990. Methadone programmes began in 1981 and soon reached approximately 80% of all IDU, but the average dosage supplied to individuals was still increasing in the 1990s. The incidences of both HIV and HCV have also declined very strongly, recently nearing zero, among Amsterdam IDU [11]. HIV prevalence has almost halved since 1990, while HCV prevalence showed a moderate decline.

To what extent this reduction in disease spread can be attributed to these interventions is unclear; the epidemics have progressed naturally and other, possibly important, factors have changed over time in Amsterdam. While at the beginning of the HIV epidemic the IDU population was increasing, in recent years fewer individuals have begun injecting [12]. This has caused shifts in the age distribution and possibly related shifts in the risk of acquiring infection. Since 1996, HIV treatment by combination antiretroviral therapy (cART) became widely available. Furthermore, mortality linked to risk behaviour, saturation effects and interaction of the two infections may have played a role.

In this study we report on the results of an individual-based modelling study. Model parameters were based on data collected in the Amsterdam Cohort Studies (ACS). We investigated the distinct effects of various factors, including demographic parameters, by simulating alternative scenarios. Model predictions were compared to the observed patterns of HIV and HCV incidence and prevalence in the Amsterdam IDU population. In particular, we considered whether the decline in HIV and HCV spread could be explained without assuming effects of harm reduction.

METHODS

An individual-based model

We implemented an individual-based model describing demographic changes and infection dynamics of HIV and HCV. Individuals entered the model at the beginning of their injecting career; subsequently they could stop injecting, relapse, acquire HIV and/or HCV and die or leave the population. Age and time since acquiring infections were updated each month. The population was divided into individuals who, throughout their injecting career, engaged in high-risk behaviour (sharing many syringes) and those taking a lower risk (sharing fewer syringes) [13]. An individual's probability of acquiring infection depended on their syringe-sharing rate and the probability that a borrowed syringe came from an infected IDU, determined by population prevalence. The individual rates of borrowing and lending out syringes were assumed to be equal. A separate parameter determined whether or not IDU were more likely to borrow syringes from individuals of their own risk type. For model implementation and details, please refer to Appendix S1.

Model parameters

The ACS

We estimated demographic parameters from the Amsterdam Cohort Studies among drug users [14]. Recruitment for this open cohort study started in 1985, and took place at methadone outposts, the weekly sexually transmitted diseases (STD) clinic for drug-using prostitutes and by word of mouth. Participants were interviewed in principle every 4 months (6 months since 2003). Blood samples were also taken at each visit, from which HIV and HCV antibody status were determined. Note that the latter did not distinguish chronic from naturally resolved HCV infections [15].

IDU population

Population inflow in the model was based on back-calculations from the number of participants in methadone programmes [16]. Injecting drug use began in 1960 and was especially popular from 1970 until 1985, but inflow has declined strongly since then. Compared to the overall Amsterdam IDU population, ACS participants began drug use somewhat later (Fig. 1). This is probably a consequence of an inclusion criterion selecting for recent drug use; those who stopped using drugs before the ACS started were excluded. We incorporated this potential bias by explicitly modelling ACS participation, each year enrolling a number of current IDU equal to the actual ACS inclusion number.

IDU may go through many cycles of ceasing injecting and subsequent relapse. In the model, the stop injecting probability was 0.016 and the relapse probability was 0.004 per month. These probabilities gave an adequate fit to the fraction of recent injectors among ever-IDU and to the average duration of injecting within the ACS (see Supplementary Fig. S2).

The mean age at first injection for ACS participants was 22.3 [standard deviation (SD) 6.4] years. Effort has been put into tracing individuals no longer participating in the ACS; for example, by matching against the population register. From these data we estimated that individuals had a monthly probability of 0.0007 to leave the population by moving out of Amsterdam. We did not find that this rate differed between HIV-infected and -negative individuals.

Incidence was defined as the fraction of uninfected ever-IDU becoming infected. AIDS was first reported in Amsterdam in 1982 [17], and a first IDU acquired immunodeficiency syndrome (AIDS) case was reported in 1985

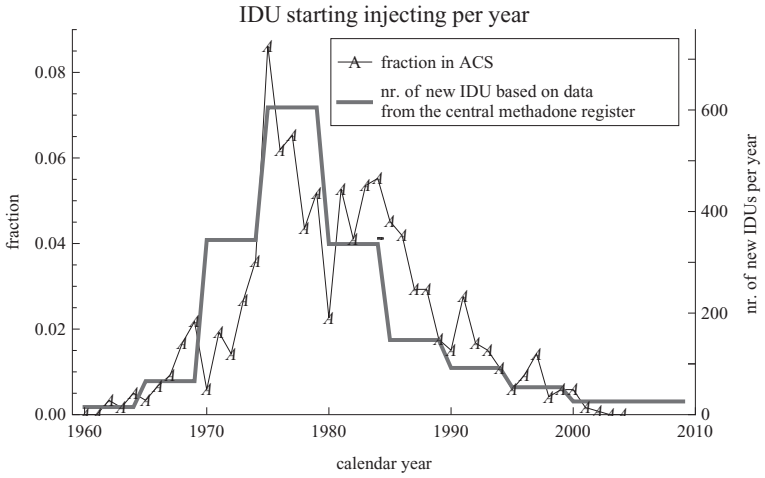


Figure 1 The fraction of all Amsterdam Cohort Study (ACS) participants who started injecting within a particular calendar year compared to the estimated inflow of new injecting drug users (IDU) per year based on data from the central methadone register of Amsterdam (from [16]). This last information was used to calculate the number of new injectors per month in the model. The ACS started in 1985 and current drug use (although not necessarily injecting) was a condition of inclusion, but not of continued participation

[18]. We therefore entered 30 HIV-infected individuals in 1980. Because HCV has been circulating for a long time and is universally present in IDU populations [19], we gave new IDU entering the model a 0.1 probability to be HCV-infected from the start of the injecting epidemic in 1960 up to 1970. At all other times, individuals were HIV- and HCV-negative at model entrance.

Mortality

Age-dependent all-cause mortality rates for HIV-negative IDU in the ACS were determined by performing Poisson regression analysis on monthly survival status using R version 2.14.1 [20]. Follow-up time was divided into recent injecting versus non-recent injecting, based on whether or not injecting episodes were reported in an individual's last interview. Mortality rates for those recently injecting were higher than for those who had stopped injecting, especially for individuals in their 20s (see Supplementary Fig. S1). Rates increased strongly for all IDU aged 50 years or older. For IDU included in the ACS, we did not find a significant association of HCV with the risk of dying.

Estimates of additional HIV-induced mortality were based on data from the CASCADE Collaboration (Concerted Action on SeroConversion to AIDS and Death in Europe), which includes 28 HIV-seroconverter cohort studies from mainly European countries [21]. These HIV-induced mortality rates depended on age and time since HIV seroconversion. cART was introduced in 1995. In high-income countries uptake increased rapidly from 1997 [22], and within the CASCADE data, HIV-induced mortality dropped somewhat abruptly at that time (Fig. 5). Presumably, those in need of treatment received treatment promptly. We therefore adjusted for cART influence on mortality at the population level, by stratifying the mortality rate by time-period before and after 1997.

HIV and HCV

Disease-specific parameters were informed from the literature (see Table 1). Transmission probabilities of HIV per sharing act of an infected syringe were based on a literature review [23]. Individuals newly infected with HIV have a higher viral load [24], and are therefore thought to be approximately 10 times more infectious [25]. This HIV acute phase lasts approximately 2 months [26]. As cART lowers viral load, the infectiousness of HIV per syringe was lowered by 10 times for those on cART [27]. A 0.0125 monthly probability to begin cART treatment from 1996 onwards provided an adequate fit to the cART uptake data within the ACS (see Supplementary Fig. S2c).

A fraction of HCV-positive IDU clears HCV spontaneously during the acute phase [28], usually within 6 months after infection [29]. HIV coinfection reduces this HCV clearance rate [15]. IDU-specific infectivity estimates for HCV are unavailable [30]. Therefore, we based HCV infectiousness per syringe on transmission of HCV to health-care workers after deep needle-stick injuries, as this should be most comparable to IDU exposure [31,32].

Risk

From a previous analysis of ACS data we concluded that there was strong heterogeneity in risk within the Amsterdam IDU population, but reliable estimates of the absolute numbers of syringes shared were difficult to obtain [13]. We therefore chose a set of risk parameters (for the baseline scenario the fraction of new IDU taking high risk throughout their injecting career, the number of syringes shared by low- and high-risk IDU and the tendency for sharing within risk groups) that explained most clearly the incidence and prevalence of HIV and HCV observed in the ACS.

Table 1 Model parameter values.

Parameter	*Value*		*Source*
Infectiousness, acute HIV	0.08 per syringe		[25]
Infectiousness, chronic HIV	0.008 per syringe		[23]
Infectiousness, HIV with cART	0.0008 per syringe		[27]
Infectiousness, HCV	0.05 per syringe		[31]
Duration of acute HCV	6 months		[29]
Duration of acute HIV	2 months		[26]
Probability of clearing HCV for HIV-negative IDU	0.25		[28]
Probability of clearing HCV for HIV-coinfected IDU	0.15		[15]
Population specific parameters			
Rate of moving from Amsterdam	0.0007		ACS
Mortality rates[a]	Supplementary		ACS and CASCADE
Monthly number of new injectors	Figure 1		[16]
Stop injecting rate	0.016		ACS[b]
Relapse rate	0.004		ACS[b]
cART starting rate, from 1996	0.0125 per month		ACS[c]
Fraction of new IDU taking high risk	0.69		ACS[d]
High-risk syringe-sharing rate	6 per month		ACS[d]
Low-risk syringe-sharing rate	0.6 per month		ACS[d]
Mixing parameter q[e]	0.7		ACS[d]
Scenario specific parameters			
No HIV treatment scenario:			
cART uptake rate	0		–
HIV-induced mortality after 1997 as before 1997	–		–
Risk-switching during individual injecting time scenario:			
Syringe-sharing rate IDU injecting <2 years	5.2 per month		ACS[d]
Syringe-sharing rate IDU injecting >2 years	0.1 per month		ACS[d]
Behaviour change over calendar time scenario:			
Calendar year-dependent risk multiplier:	Low-risk	High-risk	ACS[d]
<1979	4	2	
1979–94	1	1	
1995	0.6	1	
1996	0.4	0.9	
1997	0.2	0.8	
1998	0.05	0.7	
1999	0.05	0.3	
>2000	0.05	0.1	

Values describe the baseline scenario; for the alternative scenarios the changed or additional parameters are given. [a]Dependent on age, injecting status and HIV infection [time since HIV seroconversion and time-period before/after widespread uptake of combination antiretroviral therapy (cART)]. [b]Fitted to the fraction of recent injectors (injecting at the last interview) among ever injectors within the Amsterdam Cohort Study (ACS), the duration of injecting and the duration of injecting at first ACS visit. [c]Fitted to cART uptake among 126 injecting drug users (IDU) with known HIV seroconversion dates within the ACS. [d]Fitted to HIV and hepatitis C virus (HCV) prevalence within the ACS. [e]Parameter q gives the preference for within group sharing. If $q = 0$ sharing takes place at random, with $q = 1$ sharing occurs only within and not between subgroups. CASCADE = Concerted Action on SeroConversion to AIDS and Death in Europe.

Scenarios

We performed simulations for four scenarios to quantify the possible contributions of demographic changes to the observed changes in HIV and HCV incidence and prevalence within the ACS. In the 'baseline scenario', we assumed that there was no individual behaviour change over time, so that changes in incidence and prevalence were due only to natural epidemic progression and the changes in demographic factors (inflow and mortality), as discussed above. In the 'no HIV treatment scenario', HIV-induced mortality rates from before cART introduction were continued during the period after 1997, and also lowered HIV infectivity by cART was not included.

There are indications that beginning injectors (within about 2 years of starting injecting) might be especially prone to taking high risk, perhaps as they often borrow syringes from those who introduce them to injecting [33–35]. We therefore included a 'risk-switching during individual injecting career scenario'. For clarity, risk

heterogeneity between individuals was excluded here; all IDU began with high borrowing frequency but lowered their risk 2 years after first injecting. Again, borrowing rates were chosen in order to match observed HIV and HCV. In a 'behaviour change over calendar time scenario', we included the possible impact of harm reduction by adding to the baseline scenario a calendar year-dependent risk alteration for all IDU. This refinement in borrowing rates was also guided solely by model fit to HIV and HCV incidence and prevalence.

Per scenario, we performed 100 model runs. To compare scenarios we calculated the total of squared differences between yearly ACS data and model averages.

RESULTS

Baseline scenario

Modelled HIV incidence peaked directly after introduction in 1980 (Fig. 2). In 1990 HIV prevalence had risen to about 20% among all ever injectors, but to about 32% among modelled ACS participants. HCV prevalence rose steadily, and incidence peaked around 1970. The simulation followed the strong HIV and HCV incidence decline observed in the ACS, as well as the HIV prevalence decline up to the mid-1990s. However, it did not reproduce the decline in HCV prevalence.

We chose risk parameters that fitted the observed HIV and HCV data well. Frequent borrowing concentrated among part of the population, the high-risk subgroup, caused HIV prevalence to rise quickly, while a lower risk in the rest of the population limited the maximum HIV prevalence achieved (Fig. 3). The high prevalence of HCV within the total population indicated further that borrowing rates within the low-risk group were not negligible.

The constant stop injecting rate, coupled with a low inflow of new IDU, caused a decline over time in the fraction of the population currently injecting (Fig. 3c). There were more current injectors within the ACS, especially at the start of the cohort, due to the inclusion criterion selecting for recent injecting, explaining the higher

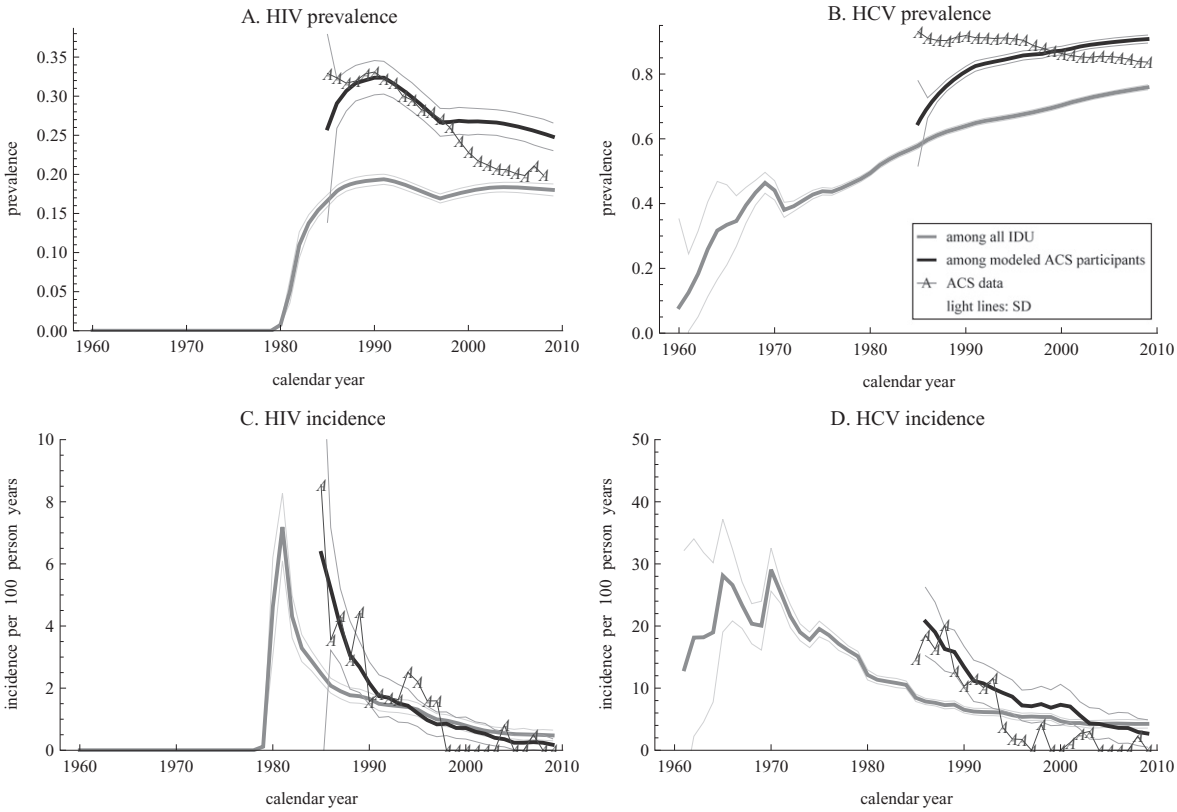


Figure 2 Infection and population dynamics in the baseline scenario from 1960 to 2010. (a) HIV prevalence. (b) Hepatitis C virus (HCV) prevalence (defined by the presence of HCV antibodies; it does not distinguish chronic from spontaneously cleared infection: see text). (c) HIV incidence. (d) HCV incidence. HIV prevalence rose quickly after introduction in 1980, peaking around 1990, and then declined. From around the time of introduction of combination antiretroviral therapy (cART) in 1997, the model overestimated HIV prevalence compared to observations in the Amsterdam Cohort Study (ACS). HCV prevalence rose more slowly and continued to increase over time, contrary to the decrease seen within the ACS. The model also somewhat overestimated HCV incidence from the mid-1990s. The average of 100 simulations is shown; lighter lines give the average ± 1 standard deviation from these 100 runs. IDU = injecting drug users

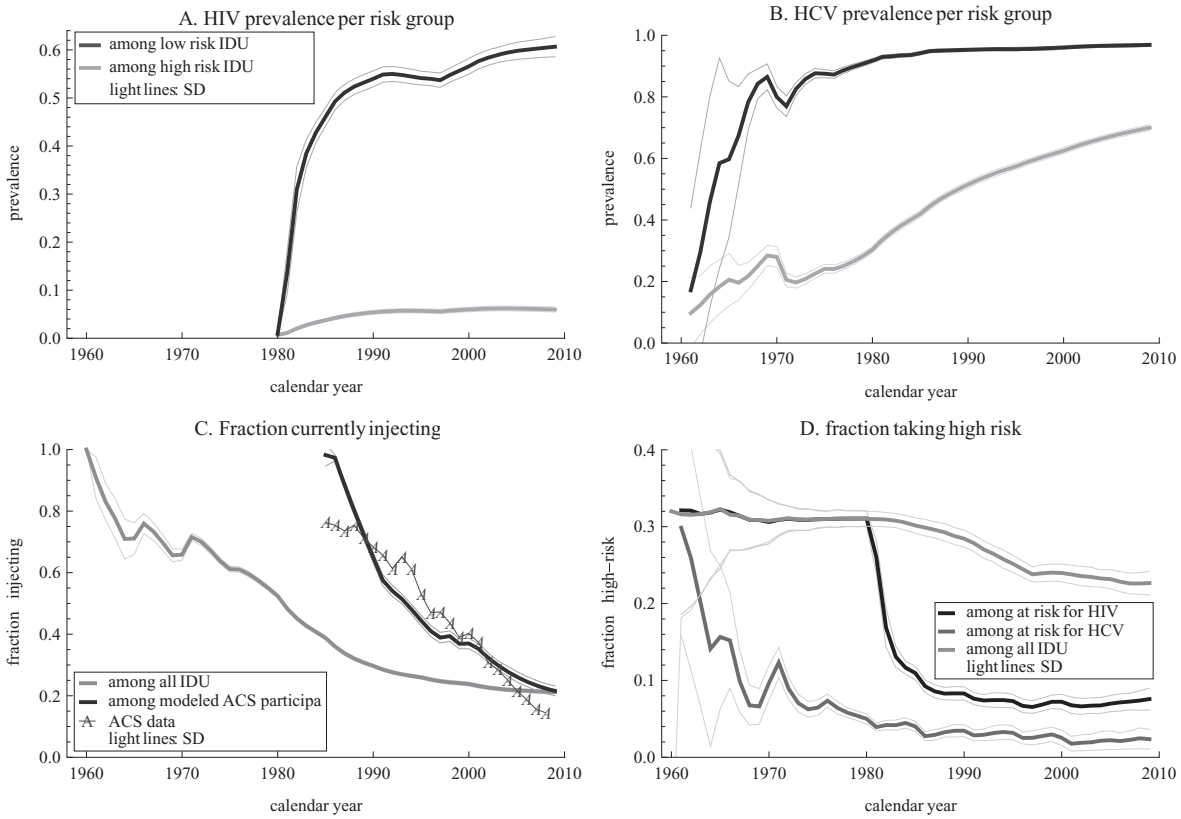


Figure 3 (a) HIV prevalence for low- and high-risk injecting drug users (IDU). (b) Hepatitis C virus (HCV) prevalence for low- and high-risk IDU. (c) Fraction of IDU currently injecting. (d) Fraction of high-risk currently injecting IDU, separately for those at risk for HIV (HIV-negative) and those at risk for HCV (HCV-negative). Few IDU with low syringe-borrowing rates became HIV infected. Most high-risk IDU became HCV infected, but high HCV prevalence was also achieved among low-risk IDU. Decline in current injecting was especially strong within the Amsterdam Cohort Study (ACS). After introduction of HIV, the fraction with high-risk behaviour among those at risk for HIV declined quickly. Subsequently, due to HIV-related mortality especially of high-risk IDU, the fraction of high-risk IDU within the total population declined as well. Baseline model parameters (see Table 1). The average of 100 simulations is shown (± 1 standard deviation)

incidence rates within the cohort compared to rates among all IDU. Incidence was lowered further because most high-risk IDU became infected early; as inflow of new high-risk IDU was limited, this lowered the borrowing rate among IDU at risk for disease (those still injecting but not yet infected) (Fig. 3d).

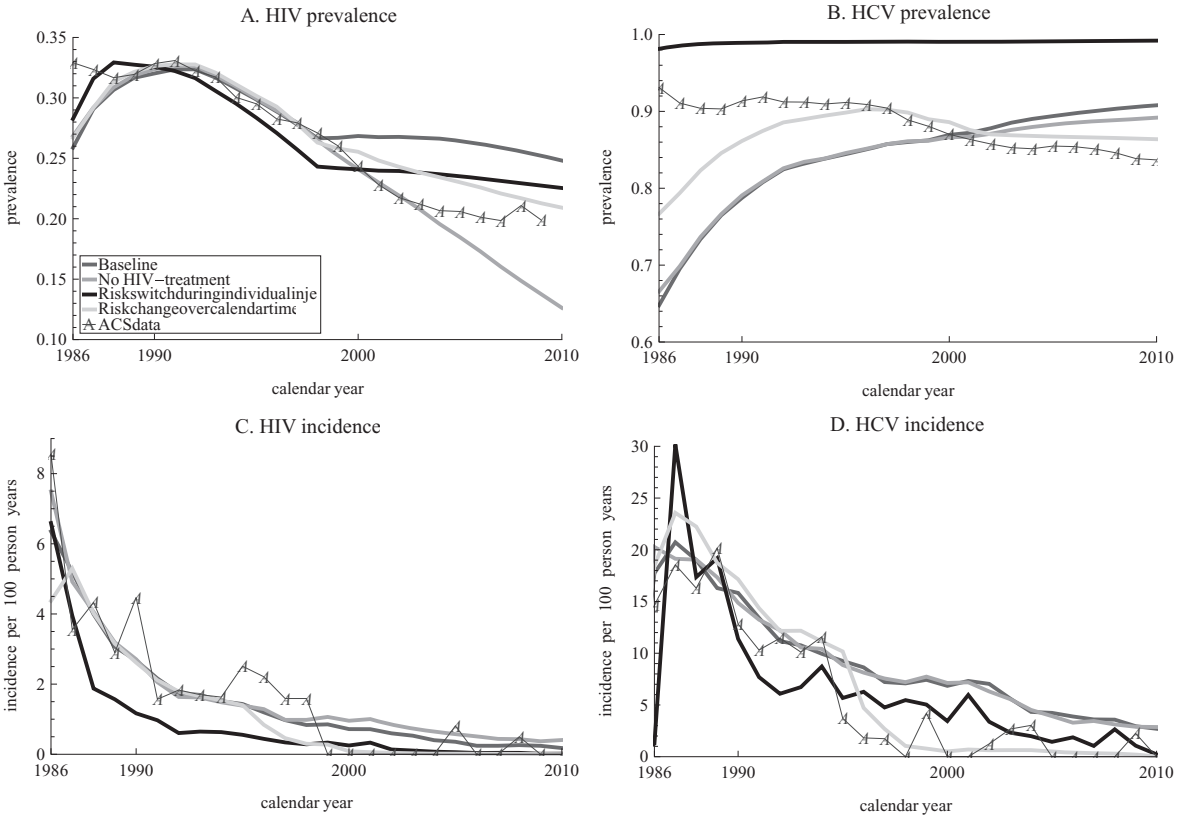
Because HIV-related mortality was concentrated within the high-risk group, population risk decreased. Not only did IDU remain at risk for disease, borrowing fewer syringes on average, when they borrowed syringes these were less likely to come from a high-risk-taking/HIV-infected IDU. This enabled a strong HIV prevalence decline within the modelled ACS. HCV prevalence was not affected greatly by population-risk decline, as the difference in HCV prevalence between risk subgroups was smaller. Rather, as injecting duration increased over time, individual cumulative risk increased, causing a continued HCV prevalence increase in the model, in contradiction with the decline seen in the ACS data.

No HIV-treatment scenario

Without cART, compared to within the baseline scenario, HIV prevalence decreased more strongly from 1997 (Fig. 4). Just after the peak of HIV prevalence in 1990, almost half of all deaths among IDU were caused by HIV (Fig. 5). Despite lowered HIV transmission, cART increased HIV prevalence by preventing mortality of HIV-infected IDU. HIV treatment had negligible effects on prevalence and incidence of HCV.

Risk-switching during individual injecting career scenario

In this scenario, early risk was set to be extremely high to allow HIV to spread quickly and reach levels comparable with ACS data, while risk later in the individuals' injecting careers was set to be very low to maximize population change in risk over time. As all IDU went through a period of high risk, HCV prevalence became high compared to ACS data (Fig. 4).



Model fit to ACS data by squared residuals (relative to baseline)	*HIV prevalence*	*HIV incidence*	*HCV prevalence*	*HCV incidence*	*Overall*
Baseline	0.033 (1)	17.4 (1)	0.255 (1)	437 (1)	1
No HIV treatment	0.016 (0.47)	15.0 (0.86)	0.231 (0.90)	422 (0.97)	0.80
Risk-switching during individual injecting	0.011 (0.33)	38.0 (2.18)	0.307 (1.20)	506 (1.16)	1.22
Risk change over calendar time	0.010 (0.30)	31.4 (1.80)	0.060 (0.24)	196 (0.45)	0.70

Figure 4 Hepatitis C virus (HCV) and HIV prevalence and incidence among modelled Amsterdam Cohort Study (ACS) participants for the different scenarios over time. The baseline scenario slightly overestimated actual HIV prevalence from combination antiretroviral therapy (cART) introduction onwards. Removing cART from the model (the no HIV treatment scenario) resulted in underestimation. These two scenarios both underestimated early HCV prevalence. Conversely, assuming all injecting drug users (IDU) went through a high-risk phase (risk-switching during individual injecting time) led to overestimation of HCV prevalence. The model fit was improved by adding risk change over calendar time; only this scenario reproduced the slight HCV prevalence decline seen in the ACS data. For model parameters see Table 1. For each scenario the average of 100 simulations is shown

HIV and HCV incidence declined strongly as the fraction of inexperienced injectors declined. The inflow of new drug users was lowered before the peak of HIV in 1990, so that most IDU were already experienced at that time (Fig. 6). With this relatively short high-risk stage, therefore, we could not explain the diminished spread of HIV and HCV prevalence seen from 1990 onwards in the ACS.

Behaviour change over calendar time scenario

The fit of the baseline model was improved (squared residuals 30% lowered) by adding strong individual behaviour change over calendar time (Figs 4 and 6). Syringe borrowing rates before 1978 in this scenario were chosen to be higher than in the baseline scenario to increase the maximum HCV prevalence reached. The risk decline at the population level from 1995 onwards caused a stronger decline in HIV and HCV incidence and HIV prevalence, as well as decline in HCV prevalence.

DISCUSSION

The main trends over three decades of HIV and HCV incidence and prevalence among Amsterdam IDU were

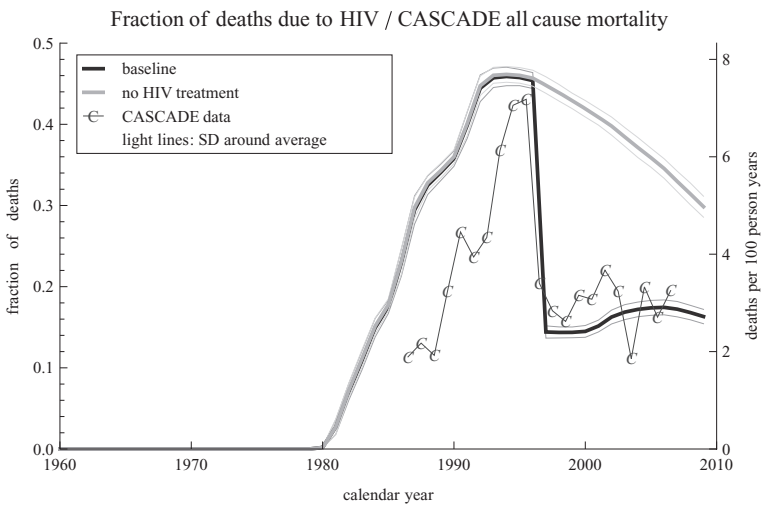


Figure 5 Fraction of overall mortality in the model which is due to HIV, and the overall mortality rate in HIV-infected injecting drug users (IDU) from the CASCADE (Concerted Action on SeroConversion to AIDS and Death in Europe) Collaboration. At the peak of HIV prevalence, around 1990, almost half of all modelled deaths were caused by HIV. The immediate lowering in HIV-related mortality from 1997 within the baseline scenario was based on the abrupt drop in mortality seen in the CASCADE data, due to the introduction of combination antiretroviral therapy (cART). For the no HIV-treatment scenario HIV-related death rates were not lowered; the relative importance of HIV-related mortality became less as HIV prevalence decreased and as average age increased (increasing the background mortality) over calendar time. For model parameters see Table 1. For each scenario the average of 100 simulations is shown

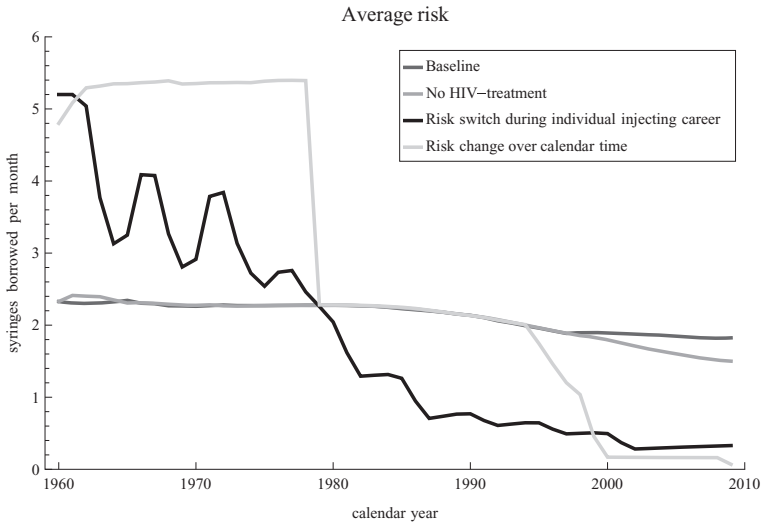


Figure 6 Average risk [number of syringes exchanged per month per injecting drug user (IDU)] in the different scenarios over time. In the baseline scenario and the no HIV treatment scenario, risk declined due to higher HIV-induced mortality among higher-risk IDU. In the risk change over calendar time scenario, we additionally imposed behaviour change, depending on calendar year. In the risk-switching during individual injecting career scenario, risk declined as the fraction of inexperienced IDU decreased (oscillations are due to inflow changing stepwise over calendar year). For model parameters see Table 1. For each scenario the average of 100 simulations is shown

reproduced by an individual-based simulation model, using information about demographic changes and disease-related mortality. The baseline scenario simulation showed a peak in HIV prevalence and a strong decline in HIV and HCV incidence, as has been observed in the ACS.

In the model, the introduction of cART resulted in a reduction of HIV incidence but increased HIV prevalence, due to increased survival of HIV-infected IDU. The instantaneous impact of cART introduction on modelled mortality was based on the abrupt drop in mortality seen in the data from the CASCADE Collaboration. However, only IDU with known seroconversion dates, many from hospital cohorts, were included in this analysis. Among drug users in Amsterdam little change in mortality was seen over time [36], implying that their cART uptake may have lagged behind. With a more gradual drop in HIV-induced mortality rates, the model better represents HIV prevalence as observed in the ACS.

We found that population risk levels could have declined even with constant risk behaviour of individuals. Active and higher risk-taking individuals would have become infected and died from HIV at an early stage of the epidemic, leaving a population with a lower average risk level. Higher mortality unrelated to HIV in the high-risk population may have enhanced that trend. Conversely, high-risk IDU were less likely to cease injecting than low-risk IDU [37], and mortality by overdose seems to be higher for occasional, less experienced, injectors [38].

Risk behaviour may also have been lowered naturally by being linked to time since first injecting. In particular, when new injectors borrowed more syringes, the diminished inflow over time led to a diminished average risk level in the population. In our analysis, without risk heterogeneity between individuals, risk heterogeneity over injecting time had to be unrealistically large to explain HIV prevalence decline fully.

The baseline model fit to the data was enhanced by assuming strong changes in risk behaviour over calendar time, related possibly to harm reduction interventions. In particular, in the ACS HCV and HIV incidence declined faster in the mid-1990s, and HCV prevalence also declined.

Our modelling approach has limitations. Unfortunately, reliable data were lacking to inform on risk behaviour parameters directly. We aimed to show how far harm reduction effects are necessary to explain disease patterns. Therefore, we conservatively chose risk values that led to good agreement of simulations and data without assumptions on reductions in risk by individuals over calendar time. This led us to assume strong risk heterogeneity, and that most syringe-sharing occurred among IDU of similar risk.

Although, over time, an estimated 15% of Amsterdam IDU participated in the ACS, this cohort might not be fully representative for all IDU. We have ignored HCV treatment in our simulations, as until recently uptake was very limited. We found no influence of HCV on IDU mortality, but it is known that ongoing HCV infection causes liver failure [39]. HCV compared to HIV infectivity is highly uncertain [30]. Also, HCV viral load is increased in early HCV infection and by HIV coinfection, which might affect HCV infectivity [40].

In dealing with these uncertainties our approach is an asset, as the influence of different assumptions could be explored in separate scenarios. Including an added HCV-induced mortality had negligible effects on the model results, as HCV has a relatively long incubation period and competing mortality was high [41]. Underestimation of HCV infectivity (for acute HCV) could explain why early HCV prevalence in the ACS was underestimated in the baseline scenario. With HCV more infectious for HIV-coinfected individuals, an extra peak in HCV incidence occurred at the rise of HIV, but in this scenario HCV prevalence did not decline together with the declining HIV prevalence. The HCV prevalence decline could be obtained by an extended individual risk decline after 2 years from starting injecting (or by age).

We focused upon qualitative understanding rather than quantitative analysis. Much complexity was included in the model, such as individual ageing, recruitment of IDU, disease-related mortality and intrinsic transmission dynamics, which allowed us to explore multiple explanations for the observed time trends. We required the model to explain simultaneously the epidemic patterns of two diseases, which restricted the number of scenarios compatible with the data.

During past decades, much evidence has been gathered on the usefulness of harm reduction interventions; for example, showing lowered HIV and HCV incidence rates for participants in programmes [6–8,42]. In a review of reviews, however, Palmateer *et al.* conclude that the evidence for prevention of HIV and HCV transmission by needle exchange programmes only was, respectively, tentative and insufficient [5]. One of the main reasons for continued uncertainty is the self-selection inherent in harm reduction participation, which impedes the drawing of causal inferences from individual-level observational research.

On a population level, demographic and epidemic stage diversity confounds the relationship between incidence rates and interventions [2]. By using mathematical modelling these complications can be addressed, but studies attempting this are rare. An example similar to our research is that of Hutchinson *et al.*, who modelled a population of IDU in Glasgow [9]. Risk behaviour in their model, however, was based directly on self-reported syringe-sharing tendencies in different time-periods, and it was assumed that the decline in this risk behaviour was due to interventions.

Our aim was to use only the relatively reliable data on incidence and prevalence to explore the evidence for the impact of harm reduction among IDU in Amsterdam. However, ACS data collection began only after widespread harm reduction programmes were initiated in Amsterdam around 1980, so that trends indicating intervention effectiveness might have been missed. Additionally, it might be argued that these programmes contributed to the decline in new individuals starting injecting, although a qualitative study found that young drug users were kept from injecting by fears of worse addiction and direct needle damage, more than by considerations of contracting disease [43].

Although the influence of harm reduction on disease spread in Amsterdam is plausible, large concurrent changes in this IDU population precluded drawing robust conclusions on causal effects. A strong decrease in risk behaviour due to intervention was in line with the data. Indeed, a full incidence decline of HIV and HCV and a decline in HCV prevalence were difficult to reproduce in a model without harm reduction. However, most of the decline in HIV and HCV incidence and HIV prevalence could, alternatively, be explained by taking into account that high-risk-taking IDU were the first to become infected and the first to die from HIV infection.

This study exemplifies that future research aimed at quantifying the benefits of interventions should not

neglect the influence of natural epidemic progression and demographic changes. Gaining more insight into the impact of these factors on the transmission dynamics of HIV and HCV could also help to target future intervention measures more effectively.

Declarations of interest

None.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1 Model formulation.

Figure S1 Death rates per month by age, separately for recent injectors and non-recent injectors. Recent injecting was defined as having reported injecting episodes for a period between interviews [in response to the question 'have you injected since your last Amsterdam Cohort Study (ACS) visit?']. Lines give the best fit for these hazards by spline Poisson regression.

Figure S2 (a) Average duration of injecting. (b) Average duration of injecting at first Amsterdam Cohort Study (ACS) visit. (c) Combination antiretroviral therapy (cART) uptake. A stop-injecting rate of 0.016 combined with a relapse rate of 0.04 provided a good fit to the variables of injecting duration, as well as to the fraction of injecting drug users (IDU) currently injecting within the ACS (main text Fig. 1). With a lower stop-rate and no relapse-rate, a similar fraction of IDU currently injecting over time could be achieved. However, in this case the distribution of current injectors became more skewed to shorter times since first injecting and, combined with the ACS inclusion criterion of recent injecting, this led to a lower modelled average injecting duration, especially at the first ACS visit (results not shown). From about 2000 onwards, extra effort was put into recruiting younger drug users for the ACS. This bias is not included in the model, as only few IDU were recruited after this time, so

that results would hardly be influenced. Within the ACS among 126 IDU with known HIV-seroconversion dates, cART was defined as at least three antiretroviral drug types. A 0.0125 probability per month from 1996 onwards to start cART provided a good fit to these data. Baseline model parameters (see Table 1). The average of 100 simulations is shown (± 1 standard deviation).

Table S1 Additional HIV-induced mortality, based on data from the CASCADE (Concerted Action on SeroConversion to AIDS and Death in Europe) Collaboration. From the mortality rates per group we have subtracted non-HIV-induced background mortality, the age-specific HIV-negative injecting drug users (IDU) mortality estimated from the Amsterdam Cohort Study (ACS).