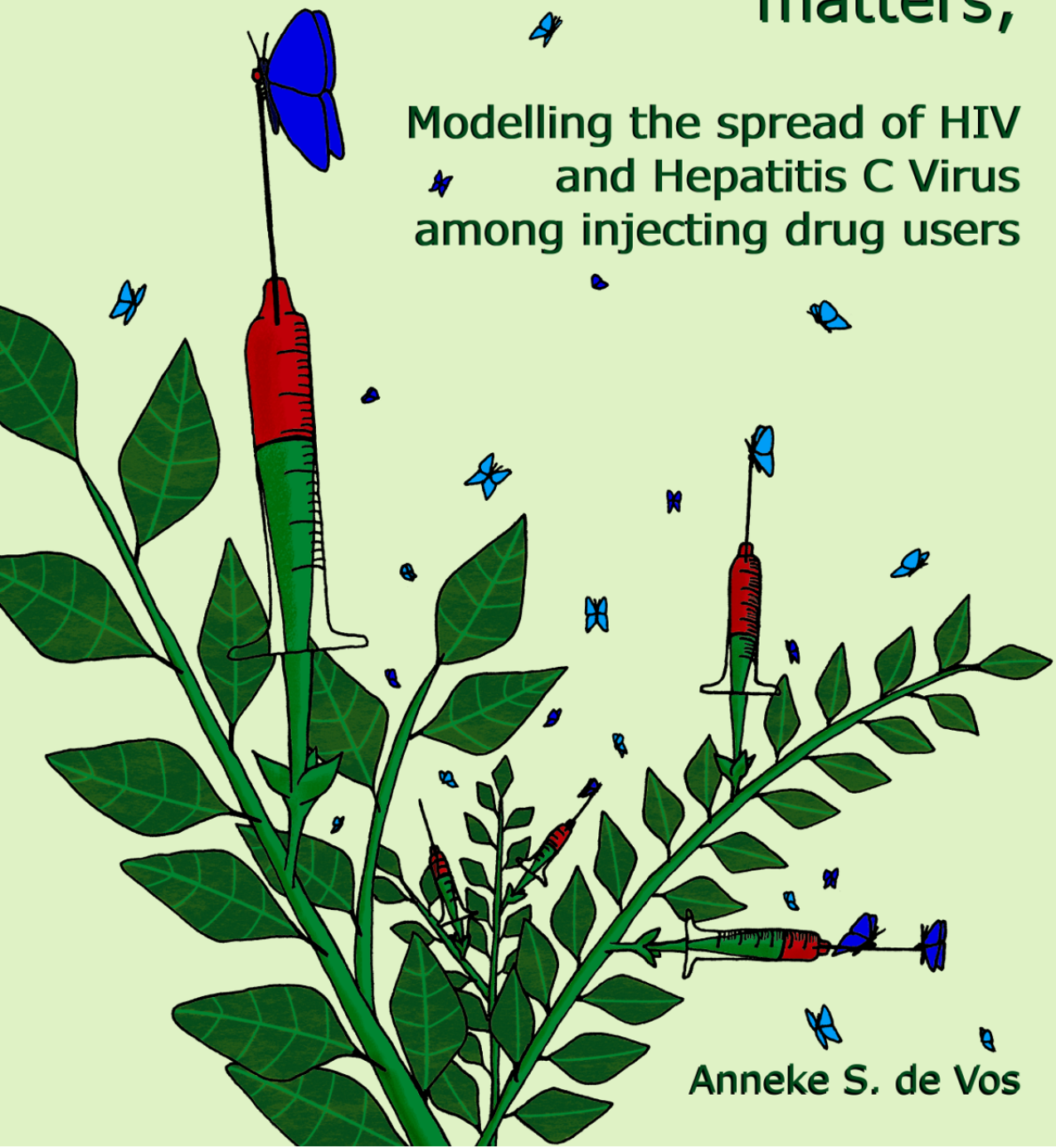
Heterogeneity in risk-behaviour matters;

Modelling the spread of HIV and Hepatitis C Virus among injecting drug users



Anneke S. de Vos

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Anneke Susanne de Vos, 2014

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Heterogeneity in risk-behaviour matters;
Modelling the spread of HIV and Hepatitis C Virus among injecting drug users

Heterogeniteit in risico-gedrag is van belang;
Modellen van de verspreiding van HIV en Hepatitis C Virus onder injecterende drugs gebruikers
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op dinsdag 28 oktober 2014 des ochtends te 10.30 uur

door

Anneke Susanne de Vos
geboren op 1 februari 1983 te Amsterdam

Promotoren: Prof.dr. M.E.E. Kretzschmar
Prof.dr. M. Prins

"Heroin" she said, "was the best I had...
No more mountains left to climb."

Wolfsheim, 1999

Contents

CHAPTER 1

General introduction; A heterogeneity in questions and models

Various viruses

It has been estimated that there are around sixteen million Injecting Drug Users (IDU*) worldwide [11]. Apart from the direct harms from drug use, including overdose morbidity and mortality, the practice of injecting has additional adverse health consequences. Namely, due to the sharing of contaminated injecting equipment blood-borne infections are spread among IDU. These infections may also be further transmitted from the IDU to the general population.

Notably HIV, the virus causing AIDS, has made many victims among IDU [11]. Outside of sub-Saharan Africa about one-third of all new HIV-infections are due to drug injecting practices, and around three million IDU are now HIV positive. Even more widespread among IDU is the Hepatitis C Virus (HCV), a cause of severe liver disease [12]. In high income countries as much as eighty per cent of new infections with this virus are due to drug injecting, and almost seventy per cent of all IDU, around ten million, have been infected with HCV [6].

In this thesis I describe how we made use of mathematical modelling to study the spread of these two viruses, including the possible impact of interventions, among people who inject drugs.

Various interventions

Especially in Europe and Australia, measures have been taken with the aim of diminishing or stopping the spread of blood-borne-infection through drug use [17]. IDU are provided with clean injecting equipment, usually needles and syringes, but sometimes also alcohol swabs, spoons and sterile water. To decrease or stop their injecting drug use, individuals may receive substitution therapy. For drug users that are dependent on opiates (such as heroin), this usually consists of a daily taken oral dose of methadone, which suppresses drug cravings and withdrawal symptoms. IDU are also provided with condoms, health promotion and risk counselling. All such measures together are called Harm Reduction policy; this is defined as management that aims to minimise the harms that drug users cause to the society and to themselves [18, 17].

A relatively new type of intervention is the use of treatment as prevention [1]. Antiretroviral treatment was developed to lower HIV morbidity, but by lowering the blood viral concentration, it also lowers infectiousness of individuals. Increasing HIV treatment uptake within a population is therefore expected to lower HIV incidence. HCV-infection can be cured by use of antivirals, and cured IDU no longer spread infection. The concept of treatment as prevention therefore also applies for this virus [10].

The current gold standard in medical research, which aims at rigorous proof of benefits from health interventions, is the use of randomised controlled trials [7]. Unfortunately, logistically as well as ethically, such research is usually not feasible for the evaluation of interventions aimed at reducing incidence among IDU [14, 19]. In observational research, incidence is compared between IDU that do and IDU that do not participate in Harm Reduction interventions. However, those that choose to receive treatment or clean syringes are likely a selective sub-group.

*Since I first started my research on this topic, it has become more commonly advocated that the term Injecting Drug Users (IDU) should be replaced by the term People Who Inject Drugs (PWID). A quote from a UNAIDS publication on terminology gives the rational: "Use person who injects drugs to place emphasis on the person first" [23]. For consistency we will use the term IDU throughout this thesis. We do realize and underline that, in contrast to the model IDU, actual individuals are more than their injecting habits and their disease status. We mean no disrespect.

Participation in Harm Reduction has also been linked to changes in risk-behaviour, as reported by the IDU themselves. Such studies are however prone to recall and reporter bias; infection status may influence recall of risk taking, and socially desirable answers may be given to please investigators or providers.

Next to comparing individuals for benefits of interventions, we may compare groups; populations of IDU from different regions under different interventions, or different overall Harm Reduction efforts. These are so called ecological studies. Alternatively, we may compare incidence rates within one population before and after the implementation of services, in a cross-over design. However, such comparisons might also be seriously biased [1].

Epidemics progress naturally; when an infection is first introduced few individuals are infectious, but incidence quickly increases with increasing prevalence of disease. Incidence strongly declines again when the pool of susceptible (not yet infected) individuals becomes depleted, and at this point prevalence will level off. There is a delay before interventions can be implemented. The lower incidence rates that are correlated with interventions may then actually be due to the comparing of populations in earlier and later epidemic stages, rather than due to the success of these interventions themselves [1].

Between populations many other factors differ as well. For example political, cultural or economic circumstances may impact on risk-behaviour. Furthermore, drug availability and IDU population size may fluctuate over time, also influencing incidence rates.

Due to the above sketched complications, uncertainty remains over the effects of Harm Reduction policy, despite much research into this topic [14]. Usefulness of comprehensive Harm Reduction programmes is acknowledged by most, since high intervention coverage is related to lower incidence [25, 22, 8, 18]. The relative contribution of the individual policy components is less certain however, and there is still much debate especially of the effects of Harm Reduction programmes on HCV incidence. This as HCV is about ten times as infectious by blood to blood contact compared to HIV, rendering its spread much more difficult to control.

These difficulties in the research can be addressed by the use of mathematical modelling. With mathematical models, we simulate risk-behaviour, interventions, and the resulting spread of infections. Natural epidemic progression and the influence of any co-occurring changes can be accounted for. Models are used to study different possible intervention scenarios, at a fraction of the costs of implementing actual trials, and without needing to wait many years for results. By indicating their optimal implementation, such models inform policy, increasing the effects while lowering the costs of interventions.

A variety of models

Different types of models are useful for studying different types of questions. Models always represent a simplification of reality, and the art of modelling lies in including those aspects of reality that are relevant to a question at hand. Very simple models may be extremely valuable in that they allow better insight into the processes governing the spread of infections; the impact of individual variables can be studied in such models. For example, we describe mechanistically how risk-behaviour, the practice of sharing syringes, translates into risk for infection. This allows us to address how the rate of syringe sharing of an IDU under intervention will impact the benefits of the intervention.

To render possible direct linking of causes and effects, we often make use of static models. This means that we simplify by assuming disease prevalence to be in a steady state, or equilibrium. Dynamic models on the other hand capture fluctuations in prevalence and incidence over time. These models commonly consist of systems of differential

equations, which describe how the fractions of susceptible and infected individuals change over time. Such models are deterministic; together with the initial population conditions, the state of the model population at any further time point is fixed. We use such population level models to describe in broad outlines the spread of infection in a generalised IDU setting.

More detailed models are useful in that we can better compare their results with the actual spread of infections within specific populations. For example, for a declining IDU population, it may be very relevant that IDU are ageing and that disease progresses over time. To capture such factors, individual level simulation models are most practical. In these models we keep track of specific individuals, updating at each time-step their characteristics such as age, disease status and risk-behaviour. Due to inclusion of chance processes, such as whether infection takes place for a specific IDU or not, each model run will be somewhat different. That is to say that these models, like the processes they mimic, are not deterministic.

Even with todays relatively high computing powers, balancing tractability and realism in models remains a main challenge. For our model studies, we are also limited by the data informing the model parameters. For example, to render a model more realistic by inclusion of individual age, the model age distribution should agree with that of the population being modelled.

For informing parameters of the models in this thesis we made much use of data from the Amsterdam Cohort Studies (ACS) among injecting drug users [21]. This still on-going study was started at the end of 1985, only a few years after the HIV epidemic started in Amsterdam. The ACS therefore represents an exceptionally long-term source of information. For all the IDU who participate, blood samples are taken in principle every four months, revealing infection status of both HIV and HCV. From interviews administered by a research nurse, information is also available on socio-demographics, level of participation in Harm Reduction services and risk-behaviour of individuals. Additionally, information on disease progression and mortality was gathered.

Using the ACS data we examined the epidemics of HIV and HCV among the Amsterdam IDU. Harm Reduction services were set up early in Amsterdam, with the rise of HIV in the 1980s [9]. The majority of the IDU receive clean syringes, and methadone is provided here in an exceptionally low threshold setting, with abstinence from injecting not a requirement. Following the establishment of comprehensive Harm Reduction programmes the incidence of both HIV and HCV strongly declined, and nowadays hardly any new HIV and HCV infections are acquired by Amsterdam IDU [25, 26]. As argued above however, such an observation may well result from confounding factors. To properly examine the causes for this diminished viral spread, we used a mathematical model.

For the Netherlands, studying the effects of harm reduction no longer seems highly urgent. Here nowadays, as in several other European countries and Australia, few new drug users inject drugs. The Amsterdam actively injecting drug user population in particular has declined from over two thousand at its peak in the early 1980s to only a few hundred individuals at present [24]. Unfortunately however, injecting drug use does continue in other parts of the world. For this reason alone studying the Amsterdam data remains highly relevant; insights gained here may improve policy elsewhere.

Injecting drug use is a serious issue now in parts of Europe, China, Russia and India [11]. There are still newly emerging injecting drug user populations in these latter regions and in Africa [4]. In the past few years a strong increase in heroin use has been observed especially in rural areas of the USA, perhaps induced by an increase in prescription of opiates as painkillers [5, 13]. Worryingly, in the UK, where a decline in injecting drug

use was also observed, a revival in injecting practices has occurred more recently [20]. This serves as a warning that an increase in injecting could reoccur, also in places such as Amsterdam.

Variability in risk-behaviour

In this thesis, since we address several different research questions, we use both more and less detailed types of models. However, one aspect of reality which we included in each of our models is the fact that IDU are not all alike with respect to risk; some individuals engage in more risk-behaviour, they share injecting equipment more frequently compared to other IDU. We also consider that IDU may be grouped according to their risk-behaviour, with individuals more likely to share with individuals of their own level of risk-behaviour. Higher risk individuals may for example meet and inject together on the street or in places such as shooting galleries [16, 27, 3].

Such heterogeneity in risk is known to greatly impact the natural course of an epidemic [2]. The existence of a so called core-group of higher risk individuals will allow for much faster initial spread of a virus through a population. Importantly, heterogeneity may enable persistence where average individual risk would not allow for continued spread of a viral disease. On the other hand, low-risk IDU become infected only rarely, limiting the eventual endemic prevalence in the population.

Heterogeneity in risk also affects effectiveness of interventions among IDU. The core-group may cause continued spread even when average risk in a population is much lowered. Therefore, models assuming homogeneous risk distribution may often lead to overly optimistic expectations for the potential of policy to eliminate viral spread. On a more positive note, by targeting interventions at specific risk types, we may greatly enhance the efficiency of these interventions.

Unfortunately, it is difficult to obtain reliable data on equipment sharing risk-behaviour directly. This is shown for example by the fact that also many IDU that deny sharing of equipment are infected with HCV [15]. For this reason, risk-behaviour is often indirectly inferred instead, from the disease spread and prevalence measured within a population. We will return to this limitation in the overall discussion of this thesis.

An important advantage of our model of Amsterdam IDU is the inclusion of both HIV and HCV spread at the same time. Since these infections share their infection route, their simultaneous inclusion diminishes the uncertainties in the model risk-behaviour parameters.

A variety of questions (outline of this thesis)

In this thesis I present our modelling research on the spread of HIV and HCV among IDU. In the second chapter of this thesis, a deterministic population model is used to study the relationship between HCV and HIV prevalence at equilibrium, as well as between HCV prevalence and the ability of HIV to invade in a population of IDU. The rationale for the latter is that HCV prevalence among IDU may be used to inform on the risk for spread of HIV.

In the third chapter we introduce a more detailed individual-based simulation model, with model parameters informed by data from the Amsterdam Cohort Study among IDU. We discuss whether the decline in disease spread that has been observed among IDU in this city can be ascribed to the Harm Reduction measures that were taken. Alternative hypotheses for the decline in HIV and HCV are carefully addressed by inclusion in the model of population changes over time.

The same individual-based model was used in chapter four to determine the effects that antiretroviral treatment has likely had on HIV incidence among the Amsterdam IDU. Such treatment greatly lowers morbidity, but additionally lowers infectiousness of individuals. Extrapolating from the Amsterdam situation, we address also what benefits could hypothetically be achieved by a test and treat intervention among IDU in demographically different settings.

In the fifth chapter, the benefit of targeting interventions by risk-behaviour is studied. For this we again use the deterministic population model, here including two risk-behaviour sub-groups. The same question is also addressed by using individual level probability calculation. The latter enhances our understanding of how risk-level of the IDU under intervention impacts the number of prevented infections. The interventions considered in this chapter are the provision of syringes to groups of IDU, and isolation, that is stopping individuals from sharing their syringes.

HCV may be cured. In the sixth chapter we use again individual level probability calculation, here to study the benefits per one IDU treated for HCV-infection. Since curing causes a loss of infectiousness, our calculation includes a quantification of the expected infections prevented to other IDU. We also take into account that the benefits of treatment are diminished by the likelihood of re-infection of the IDU that was treated. The total magnitude of the benefits is a function of the rate of syringe sharing by the treated IDU.

In the seventh chapter, we extend the analysis of chapter five by using the deterministic model with two risk sub-groups. We discuss how prevalence of HCV contamination among exchanged syringes, rather than the prevalence among the IDU, can be used to guide who we should cure first; low- or rather high-risk-behaviour IDU.

In chapter eight I summarise the results from the above studies. In chapter nine I discuss our main findings. In this discussion I address in particular the relevance of including heterogeneity in risk-behaviour in models of IDU. I give an overview of the various ways of modelling, and also of measuring such heterogeneity in actual IDU populations. I end by considering the future role of mathematical modelling in the implementation of intervention efforts.

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CHAPTER 2

Determinants of persistent spread of HIV in HCV-infected populations of injecting drug users

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Determinants of persistent spread of HIV in HCV-infected populations of injecting drug users

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ABSTRACT

Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) are both transmitted through populations of injecting drug users (IDU) by the sharing of contaminated syringes. Prevalence of HCV is high in most IDU populations, whereas HIV prevalence varies considerably across populations. Understanding the dynamics of these interacting infections may allow us to use HCV prevalence as an indicator for the risk of persistent spread of HIV.

We developed a mathematical model that describes the spread of both HCV and HIV in an IDU population. The model allows for HCV–HIV co-infection and increased disease related mortality for both infections. Using this model we investigated how HIV and HCV prevalence both depend on level and heterogeneity of injecting risk behaviour, and how HIV and HCV prevalence are related. To gain knowledge of actual risk behaviour we analysed data from the Amsterdam Cohort Study (ACS) of drug users.

We find that there is a threshold HCV prevalence at which HIV can invade into an IDU population; below threshold HIV cannot spread. This threshold depends strongly on heterogeneity of risk behaviour in the population, as well as on whether sharing is more likely to occur within or between risk behaviour groups. We find that our model agrees with the observed relationship between HCV and HIV prevalence as described by Vickerman et al. (2010), when in addition to risk heterogeneity as fitted from the ACS, we also assume that most contacts (>90%) occur amongst IDU of the same risk level (assortative mixing).

We conclude that HCV prevalence can be used as an indicator of risk for successful HIV introduction into an IDU population. However, information on risk heterogeneity is required for determining this risk, and also for designing effective prevention strategies.

Introduction

Both hepatitis C virus (HCV) and human immunodeficiency virus (HIV) are transmitted by the sharing of used syringes amongst injecting drug users (IDU). However, HCV is more easily transmitted by blood–blood contact than HIV, so that this disease is more wide-spread amongst IDU. This led Vickerman et al. (2010) to investigate the co-occurrence of both infections with the main aim of predicting population vulnerability to HIV by measuring HCV levels. The authors used published cross-sectional seroprevalence data of HIV and HCV in a wide selection of IDU populations, and conclude that "the mean IDU HIV prevalence is likely to be negligible if HCV prevalence is less than 30% (95% confidence interval 22–38%) but increases progressively with HCV prevalence thereafter".

In order to better understand and interpret this result, we analyse a model describing simultaneous occurrence of HCV and HIV in an IDU population. The model we introduce is based on previous modelling studies of HCV, and it describes risk behaviour as the amount of syringe borrowing (Vickerman et al., 2007). Population level heterogeneity in syringe sharing behaviour is modelled by subdividing the population into groups with differing rates of used syringe borrowing and lending. Additionally, the model describes mixing between risk groups ranging from a situation where sharing amongst IDU occurs randomly, to situations where sharing is more likely between IDU of similar risk behaviour.

Our main focus is how these factors affect the theoretical relationship between the basic reproduction number R_0 and endemic prevalence of HIV in a population with a given equilibrium prevalence of HCV. We base disease parameters in our model on information from the literature. Population specific parameters for risk behaviour are estimated from the prospective Amsterdam Cohort Study (ACS) study of drug users.

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Methods

A model of HCV and HIV transmission

We consider transmission of HCV and HIV in a population of IDU that is subdivided into k behavioural subgroups. We only model transmission by sharing of contaminated syringes, not other transmission routes such as sexual transmission or transmission by sharing equipment other than syringes. The subgroups are distinguished by their frequency of sharing described by a parameter $\omega_j, j = 1, \ldots, k$. Individual risk behaviour is assumed to be constant, i.e. individuals do not switch between risk subgroups. The parameter q represents the fraction of syringe sharing which takes place within risk subgroups, with the remaining fraction $1-q$ of sharing assumed to follow proportionate mixing.

For both HCV and HIV we distinguish between susceptible (S), acutely infected (I) and chronically infected (C) individuals, so that we have nine compartments per risk subgroup. Main script denotes HCV status, superscript HIV status.

With p we denote the per HCV infected syringe use probability of becoming infected with HCV. For HCV we assume that acutely and chronically infected individuals are equally infectious. For HIV acutely infected individuals are more infectious, we distinguish p^{H_A} and p^{H_C}. Individuals move out of the acute HCV phase with rate θ, where d gives the proportion of these infections being cleared and $1-d$ the proportion of infections leading to chronic HCV. Individuals co-infected with HIV have a modified probability d^H of clearing HCV. The rate of leaving the acute HIV phase is given by θ^H.

We assume a constant recruitment rate B_j into subgroup j, and a constant rate of leaving the population μ that is equal for all groups. This last parameter is a combination of background mortality and a rate at which individuals stop injecting drug use. Furthermore, μ^+ is the additional death rate for chronically HCV-infected IDU, and μ^H the added death rate caused by HIV.

We introduce the notation $N_j = S_j^S + S_j^I + S_j^C + I_j^S + I_j^I + I_j^C + C_j^S + C_j^I + C_j^C$ for $j = 1, \ldots, k$ and $N = \sum_{j=1}^k N_j$. Furthermore

$$f_j = \frac{N_j}{N},\ \pi_j = \frac{I_j^S + I_j^I + I_j^C + C_j^S + C_j^I + C_j^C}{N_j},\ \text{and}\quad \pi = \sum_{j=1}^k f_j \pi_j \tag{1}$$

where f_j is the fraction of individuals within subgroup j, π_j the endemic prevalence of HCV in subgroup j, and π the endemic prevalence of HCV in the overall IDU population. Assuming that individuals' rates of lending out syringes equal their borrowing rates we define the probability m that a randomly borrowed syringe carries HCV infection as

$$m := \frac{\sum_{j=1}^k \omega_j f_j \pi_j}{\sum_{j=1}^k \omega_j f_j} \tag{2}$$

The force of HCV infection λ_j can now be defined as

$$\lambda_j = \omega_j p(q\pi_j + (1-q)m) \tag{3}$$

Analogously, we denote the endemic prevalence of acute HIV by $\pi_j^{H_A} = (S_j^I + I_j^I + C_j^I)/N_j$ and the endemic prevalence of chronic HIV by $\pi_j^{H_C} = (S_j^C + I_j^C + C_j^C)/N_j$. Then the probability that a randomly borrowed syringe carries HIV from acute infection is $m^A = \sum_{j=1}^k \omega_j f_j \pi_j^{H_A} / \sum_{j=1}^k \omega_j f_j$ and that it carries HIV from chronic infection is $m^C = \sum_{j=1}^k \omega_j f_j \pi_j^{H_C} / \sum_{j=1}^k \omega_j f_j$. The force of infection for HIV is then given by

$$\lambda_j^H = \omega_j p^{H_A}(q\pi_j^{H_A} + (1-q)m^A) + \omega_j p^{H_C}(q\pi_j^{H_C} + (1-q)m^C) \tag{4}$$

The model is now defined by the system of equations for $j = 1, \ldots, k$

$$\frac{dS_j^S}{dt} = B_j + d\theta I_j^S - S_j^S(\mu + \lambda_j + \lambda_j^H) \tag{5}$$

$$\frac{dS_j^I}{dt} = \lambda_j^H S_j^S + d\theta I_j^I - S_j^I(\mu + \lambda_j + \theta^H) \tag{6}$$

$$\frac{dS_j^C}{dt} = \theta^H S_j^I + d^H \theta I_j^C - S_j^C(\mu + \mu^H + \lambda_j) \tag{7}$$

$$\frac{dI_j^S}{dt} = \lambda_j S_j^S - I_j^S(\mu + \lambda_j^H + \theta) \tag{8}$$

$$\frac{dI_j^I}{dt} = \lambda_j S_j^I + \lambda_j^H I_j^S - I_j^I(\mu + \theta + \theta^H) \tag{9}$$

$$\frac{dI_j^C}{dt} = \lambda_j S_j^C + \theta^H I_j^I - I_j^C(\mu + \mu^H + \theta) \tag{10}$$

$$\frac{dC_j^S}{dt} = (1-d)\theta I_j^S - C_j^S(\mu + \mu^+ + \lambda_j^H) \tag{11}$$

$$\frac{dC_j^I}{dt} = (1-d)\theta I_j^I + \lambda_j^H C_j^S - C_j^I(\mu + \mu^+ + \theta^H) \tag{12}$$

$$\frac{dC_j^C}{dt} = (1-d^H)\theta I_j^C + \theta^H C_j^I - C_j^C(\mu + \mu^+ + \mu^H) \tag{13}$$

A flowchart of this model for one subgroup j is shown in Fig. 1.

HCV equilibria

We are interested in whether HIV can invade into a population with HCV at a certain endemic steady state. Therefore we first consider the above model with HIV in its disease free steady state, and ask under what conditions HIV can establish itself. This question amounts to determining the basic reproduction number R_0 for HIV given an endemic HCV prevalence.

For the model without HIV a relatively simple implicit solution for the equilibrium HCV prevalence π_j^* can be given as a function of the equilibrium force of infection λ_j^*. Using that $p_j^* = 1 - S_j^*/N_j^* = 1 - 1/(1 + I_j^*/S_j^* + C_j^*/S_j^*)$ we get for $j = 1, \ldots, k$

$$\pi_j^* = \frac{\lambda_j^*}{\lambda_j^* + x} \quad \text{with} \quad x = \frac{(\mu + \mu^+)(\mu + \theta)}{(\mu + \mu^+ + (1-d)\theta)} \tag{14}$$

Note that every λ_j^* is a function of all $\pi_1^*, \ldots, \pi_k^*$ as given in Eq. (3). Due to this interdependency of the π_j^*, explicit solutions become intractable for multiple groups. However, it can be shown that for any number of groups a unique positive HCV equilibrium exists above a certain threshold of risk behaviour. We do not here investigate this HCV threshold as we are interested in the dynamics of HIV against the background of an endemic HCV prevalence. HCV is much more infectious than HIV, therefore one usually finds that HCV is present in a population at endemic levels when HIV first enters the population.

From Eq. (14) we see that the equilibrium prevalence in each subgroup saturates to 1 with increasing force of infection (that is with increasing borrowing rate ω_j and population prevalence), and that prevalence decreases with increasing x. x is a combined rate of leaving the infected compartments, which increases with an increasing death rate $\mu + \mu^+$ and probability of clearing d. For a single homogeneous group, (or when groups are completely segregated, $q = 1$) the explicit solution is $\pi_j^* = 1 - x/p\omega_j$ or $\pi_j^* = 0$. This implies that HCV is endemic if the condition $p\omega_j > x$ is fulfilled.

λ_j depends on the relative sizes of the risk subgroups. For constant recruitment rates B_j the sizes of the subgroups will converge

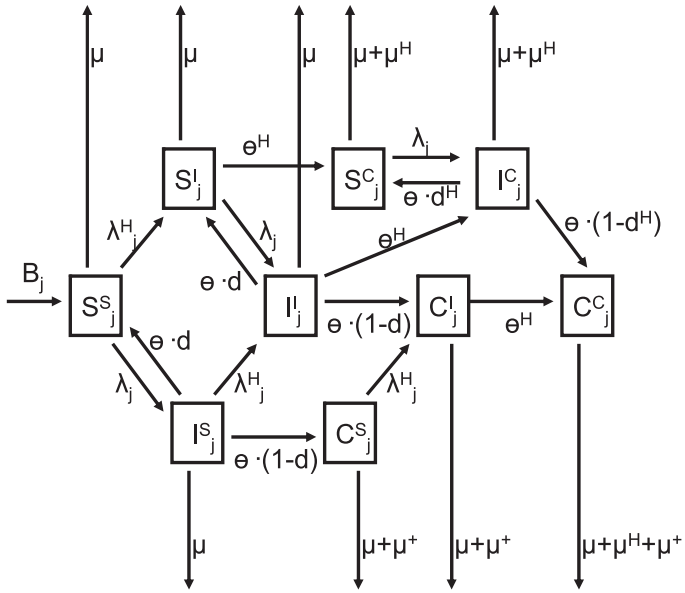

Fig. 1. A model for demographic dynamics of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) (see text).

to a constant equilibrium fraction f_j^*. For the disease free equilibrium $f_j^* = B_j/B$ with $B = \sum_{j=1}^{k} B_j$. By HCV mortality relative sizes of the higher risk taking subgroups are lowered in equilibrium, so that the f_j^* should depend on the HCV equilibrium π. However, in order to more clearly define and research risk heterogeneity, in numerical calculations we chose to define equilibrium subgroup fractions f_j^* directly, thereby only implicitly defining inflow rates B_j.

This choice is justified by the fact that those equilibrium fractions of IDU in different subgroups can be compared with population-based data on risk behaviour. In contrast, information on inflow of IDU into a population is hard to measure and inherently uncertain. However, as HCV has a relatively small influence on IDU life-expectancy, inflow and equilibrium risk group fractions should be very similar for populations affected by this disease only.

Numerical results are obtained by simulation. For simulation we used Mathematica 7.0.

The basic reproduction number R_0 for HIV

The basic reproduction number R_0 for HIV is defined as the expected number of new HIV infections caused during the infected lifetime of a typical HIV-infected individual, when HIV prevalence in the population is negligible (Diekmann et al., 2010). An HIV epidemic is expected only for $R_0 > 1$. The expected infected lifetime of an HIV-infected individual depends on the probability of co-infection with HCV, which in turn depends on the individual's risk behaviour and on the HCV prevalence. We assume HCV is at equilibrium and therefore the probability of being HCV-infected at infection with HIV for an individual of subgroup j is given by the HCV prevalence π_j^* for all j.

An individual not HCV-infected at the time of HIV infection can acquire co-infection with HCV during the course of HIV infection. The cumulative probability of co-infection with HCV is dependent on the time since infection with HIV. As HIV prevalence is still negligible the rate of acquiring HCV, λ_j^*, is unaltered from the HCV model discussed above. We denote the time since HIV infection by τ. Within a subpopulation j, the probability of being alive and HCV susceptible at time τ is denoted by $P^s(\tau)$, being alive and having an acute HCV infection by $P^i(\tau)$, and being alive and suffering chronic HCV infection by $P^c(\tau)$. These probabilities change according to

$$\frac{dP_j^s}{d\tau} = -\lambda_j^* P_j^s - (\mu + \mu^H) P_j^s + d^H \theta P_j^i \tag{15}$$

$$\frac{dP_j^i}{d\tau} = \lambda_j^* P_j^s - \theta P_j^i - (\mu + \mu^H) P_j^i \tag{16}$$

$$\frac{dP_j^c}{d\tau} = (1 - d^H)\theta P_j^i - (\mu + \mu^H + \mu^+) P_j^c \tag{17}$$

μ^H is the added death rate caused by HIV, d^H describes the proportion of HIV-infected individuals clearing HCV. At time of HIV infection, $\tau = 0$, the probability of being HCV uninfected is $P_j^s(0) = S_j^*/N_j^*$, the probability of chronic HCV infection $P_j^c(0) = C_j^*/N_j^*$, and the probability of acute HCV infection $P_j^i(0) = I_j^*/N_j^*$.

P^a denotes the probability of being alive at time τ after HIV infection, $P_j^a(\tau) = P_j^s(\tau) + P_j^i(\tau) + P_j^c(\tau)$. We denote the per contaminated syringe probability of infecting another IDU as $p^H(\tau)$. The rate of causing new infections in other IDU is then given by $p^H(\tau)\omega_j$. As infectiousness differs between acute and chronically HIV infected IDU, this infection rate is a step function with infectivity p^{H_A} lowered to infectivity p^{H_C} at transition into the chronic stage. This infection rate multiplied by the survival probability, integrated over all τ, gives the expected number of new infections caused during the entire lifetime of an infected individual. We can now write the next generation matrix $R_0(i, j)$ in which i corresponds to the risk subgroup of the infecting individual, and j corresponds to the risk subgroup of those who become infected as

$$R_0(i,j) = \int_{\tau=0}^{\tau=\infty} P_i^a(\tau) p^H(\tau) \omega_i d\tau \left((1-q) \frac{f_j^* \omega_j}{\sum_{l=1}^{k} f_l^* \omega_l} + \delta_{i,j} q \right) \tag{18}$$

where $\delta_{i,j}$ denotes the Kronecker delta, i.e. $\delta_{i,j} = 0$ for $i \neq j$ and $\delta_{i,j} = 1$ for $i = j$. R_0 is the dominant eigenvalue of this next generation matrix (Diekmann et al., 2010). This dominant eigenvalue is a weighted average of the contributions to transmission of the different types of IDU, which takes into account that certain individuals are more likely to be infected early in the epidemic than others.

Data analysis

Parameters

Parameter values used for simulation are obtained from literature. For an overview of these see Table 1.

Transmission probabilities of HIV per sharing act of an infected syringe are based on a literature review (Baggaley et al., 2006). Individuals newly infected with HIV have a higher viral load and are therefore thought to be more infectious, as has been shown for transmission by sexual contact (Attia et al., 2009; Hollingsworth et al., 2008). Infectiousness of HIV per syringe is assumed to be about ten times higher in acute compared to chronic infection (Cohen, 2006). The HIV acute phase lasts about 2 months, the rate of leaving the acute HIV phase θ^H is therefore taken as 1/2 per month (Pilcher et al., 2007).

The HCV acute phase lasts about 3 months, the rate of leaving the acute HCV phase θ is therefore taken as 1/3 per month (Lewis-Ximenez et al., 2010). A fraction of HCV positive IDU spontaneously clear HCV during the acute phase (Micallef et al., 2006). A HIV co-infection reduces the rate of HCV clearance (van den Berg, 2009). IDU specific infectivity estimates are lacking for HCV (MacDonald et al., 1996). We base HCV infectiousness per syringe on information on transmission of HCV to health care workers after needle-stick injuries, taking estimates for procedures involving hollow-bore needle placement in the source patient's vein or artery and deep injuries for the health care worker, as these should be most comparable to IDU exposure (De Carli et al., 2003; Yazdanpanah et al., 2006). As we could not find a clear indication that those with acute HCV are more infectious than those with chronic HCV, we assumed that this is not the case.

The parameter μ is a combination of the death rate of uninfected IDU and a rate at which individuals leave the IDU population by ceasing injecting drug use (Vickerman et al., 2007). $\mu = 0.0083$ implies uninfected individuals will on average remain alive and injecting for about 10 years. This injecting career length might vary strongly between populations. With a longer average injecting duration individuals remain infective longer, causing prevalences of both HCV and HIV to increase. Additional death rates of HIV and HCV are based on survival after seroconversion, assuming no antiviral treatment (Smit et al., 2006).

Risk parameters

Risk behaviour in the model is defined as the rate of borrowing and lending out of syringes. Risk behaviour and risk behaviour distribution will differ between populations, and we aim to study the effects that these variables will have on the HCV HIV relationship. However, for some indication of realistic risk values, in particular risk heterogeneity, we have analysed data from the Amsterdam Cohort Studies (ACS) amongst drug users (http://www.amsterdamcohortstudies.org/menu/reports/ACSoverview2006.pdf).

Within the standard questionnaire used in this study, IDU are asked when they have last borrowed a syringe from another IDU. Answers to this question are possible in five categories for the time period. For use in our model this information had to be translated to rates. We achieved this by fitting a model with a constant borrowing rate to the categorized data using maximum likelihood estimation (see Appendix A).

IDU participating in the ACS are also asked when they have last lent out a used syringe to another IDU. Answers for lending and borrowing are strongly correlated (Pearson correlation 0.809 with $p<0.0005$, excluding the answer "never" and including only IDU who had injected drugs since their previous visit). Therefore, we assume that the rate of syringe borrowing for individual IDU is the same as the rate of lending out used syringes to other IDU. Note that this assumption was used in the definition of m in Eq. (2), which denotes the probability that a randomly borrowed syringe carries infection.

Within social networks peer pressure can cause risk behaviour of interacting members to become similar (De et al., 2007). Individuals with similar risk behaviour may preferentially meet, for example in venues such as shooting galleries. Also, segregated groups may form based on ethnicity, within which a set of cultural rules influences the risk behaviour (Aitken et al., 2008). For Amsterdam, no information was available on how much of borrowing takes place preferentially within risk subgroups. Therefore, we examined the influence of the mixing parameter q over its total range [0,1].

Results

Influence of risk heterogeneity on HCV prevalence and HIV invasion

We investigated the influence of increasing risk heterogeneity independently from the influence of average risk levels $\sum_{j=1}^{k} f_j \omega_j = \overline{\omega}$, i.e. we varied the distribution of risk levels in the population whilst keeping $\overline{\omega}$ constant.

The basic reproduction number R_0 of HIV increases almost linearly with average risk in a population (see Fig. 2a). When HCV does not influence the death rate, this relationship is exactly linear. HCV induced mortality lowers the R_0 of HIV by decreasing the survival probability of infected individuals. However, as the HCV induced death rate is small compared to the HIV induced death rate this effect is small.

When we divide the population into a low risk and a high risk group, we see that this increases R_0. The lifetime number of new infections caused by a single infected individual from group j in an HIV naive population increases at most linearly with ω_j (see Eq. (18)). However, the increase in ω_j is magnified by an increase in weight and therefore increase in contribution to the weighted average over contributions from all risk groups that R_0 represents as the eigenvalue of the next generation matrix. An individual infected early on in the epidemic is more likely to be an individual with higher risk behaviour, that is an individual who borrows more syringes. As these same individuals will also more frequently lend out syringes, more infections result.

Increase in q, i.e. more assortative mixing, will lead to high risk taking IDU spreading HIV more often to other high risk taking IDU within the HIV naive population, which means that an individual infected early in the outbreak is even more likely to be a high risk taking individual. This increases the R_0 of HIV further.

The equilibrium prevalence of an infection saturates with increase in average risk (see Fig. 2b). For a large range of average risk values, HCV equilibrium prevalence decreases with increasing heterogeneity. The reason is that concentrating risk within part of the population results in greater saturation of risk within this higher risk subgroup. With increase in q, high risk taking IDU lend more syringes to other high risk IDU, who are more likely to already be infected. In other words, increase in q enhances saturation of prevalence with risk, so that HCV prevalence is decreased.

Table 1
Parameters and their values as used for the numerical results.

Parameter	Value	Description	Source
θ	0.33 per month	Loss rate of HCV acute status	Lewis-Ximenez et al. (2010)
θ^H	0.50 per month	Loss rate of HIV acute status	Pilcher et al. (2007)
d	0.26	Probability of clearing HCV for HIV free IDU	Micallef et al. (2006)
d^H	0.15	Probability of clearing HCV for HIV-infected IDU	van den Berg (2009)
p^{H_C}	0.008 per syringe	Infectiousness chronic HIV	Baggaley et al. (2006)
p^{H_A}	0.08 per syringe	Infectiousness acute HIV	Cohen (2006)
p	0.05 per syringe	Infectiousness HCV	De Carli et al. (2003), Yazdanpanah et al. (2006)
μ	0.0083 per month	Death and stop injecting rate for uninfected IDU	Vickerman et al. (2007)
μ_+	0.002 per month	Additional death rate due to HCV infection	Smit et al. (2006)
μ^H	0.0049 per month	Additional death rate due to HIV infection	Smit et al. (2006)
ω^l	0.65 syringes per month	Low risk	ACS[a]
ω^h	4.76 syringes per month	High risk	ACS[a]
f^l	0.58	Low risk fraction size	ACS[a]
q	0[b]	Preferential mixing within groups	–

[a] Based on data from the Amsterdam Cohort Studies on time since last borrowing from 1986 to 1990 (see Appendix A.)
[b] Information on q is lacking, we therefore take random mixing as our baseline value.

Only at low average risk can heterogeneity in risk lead to an increase in HCV prevalence, for reasons similar to the increase seen in R_0 for HIV. Average risk may be too low to sustain an epidemic in an homogeneous population, but concentrating risk in a high risk group enables persistent spread of HCV. Note that increase in heterogeneity will always lead to decrease in prevalence when lending and borrowing are uncorrelated at the individual level, i.e. when $m = \pi$ and $q = 0$ (Andreasen, 2011). In this case also R_0 is not increased by heterogeneity.

As hepatitis C is more infectious through blood–blood contact than HIV, prevalence of this infection is at saturation level of prevalence for lower risk levels. This greater saturation of risk causes HCV to be affected by risk heterogeneity in a different way than HIV. Where HIV prevalence can increase with increasing heterogeneity, HCV prevalence may decrease.

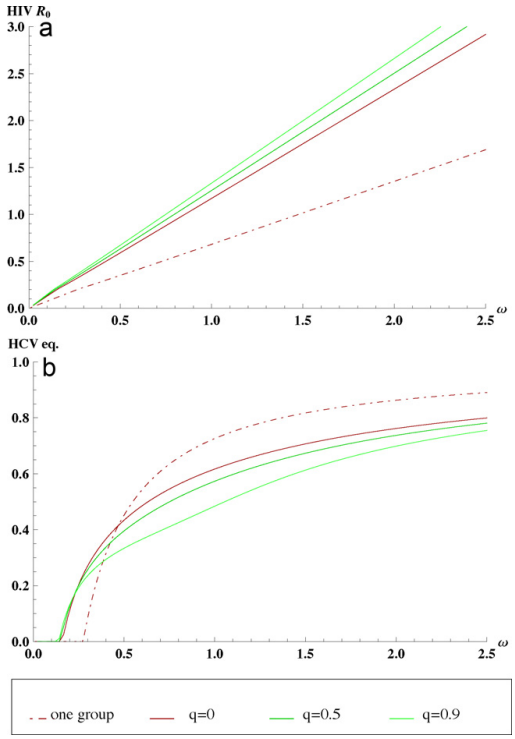

Fig. 2. (a) The basic reproduction number R_0 for HIV as a function of average risk $\overline{\omega}$ in the population and (b) the HCV equilibrium prevalence by average risk $\overline{\omega}$. Both are plotted for different values of the mixing parameter q, which describes the fraction of syringes preferentially shared within risk groups. The dot dashed line represents a population without risk heterogeneity, the other lines represent a population that is divided into a high risk and a low risk group, with fractions $f_l = 0.58$ and $f_h = 0.42$ respectively, and risk $\omega_h = 7.3\omega_l$ (for all other parameter values see Table 1).

The relationship between HCV equilibrium and HIV R_0

When increasing the total risk level whilst keeping the distribution of risk within the population constant both HCV prevalence and the R_0 of HIV increase. To study the impact of changing risk distribution with constant total risk level we define a base case using parameter values for risk heterogeneity as estimated from the ACS data, that is $f_h = 0.58$ and $\omega_h/\omega_l = 7.3$ (see Appendix A). In this case, with $q = 0$, we find $R_0 = 1$ (the threshold above which HIV can persistently spread) at about 0.6 HCV equilibrium prevalence (see Fig. 3a).

We change heterogeneity from the base case value by changing the ratio of high to low syringe borrowing rates ω_h/ω_l. With increasing heterogeneity R_0 for HIV increases and HCV prevalence decreases, as explained above. This implies that the HCV equilibrium prevalence at which HIV can establish itself is lowered. Similarly, an increase in q increases R_0 and decreases HCV equilibrium prevalence, therefore also lowering the HCV value at which R_0 is at threshold value 1 (see Fig. 3b).

Another factor influencing the HCV equilibrium prevalence at which R_0 for HIV crosses the threshold of 1, is the relative size of the risk groups (see Fig. 3c). In general, a smaller high risk group f_h allows HIV to invade at lower HCV equilibrium prevalence. A small high risk group has little influence on the overall prevalence of HCV, but may enable HIV to spread. At even smaller f_h the threshold of HCV at which HIV invades will increase again, as the high risk group becomes too small to sustain an HIV epidemic in this case. Mathematically, as f_h approaches 0 we regain a model without risk heterogeneity.

HIV in equilibrium

In the above we have focussed on the question of how HCV equilibrium prevalence may indicate whether HIV is able to invade in an IDU population, which is best answered by considering the basic reproduction number R_0 for HIV. We now turn to the relationship of HCV and HIV prevalence when HIV can establish itself as an endemic infection.

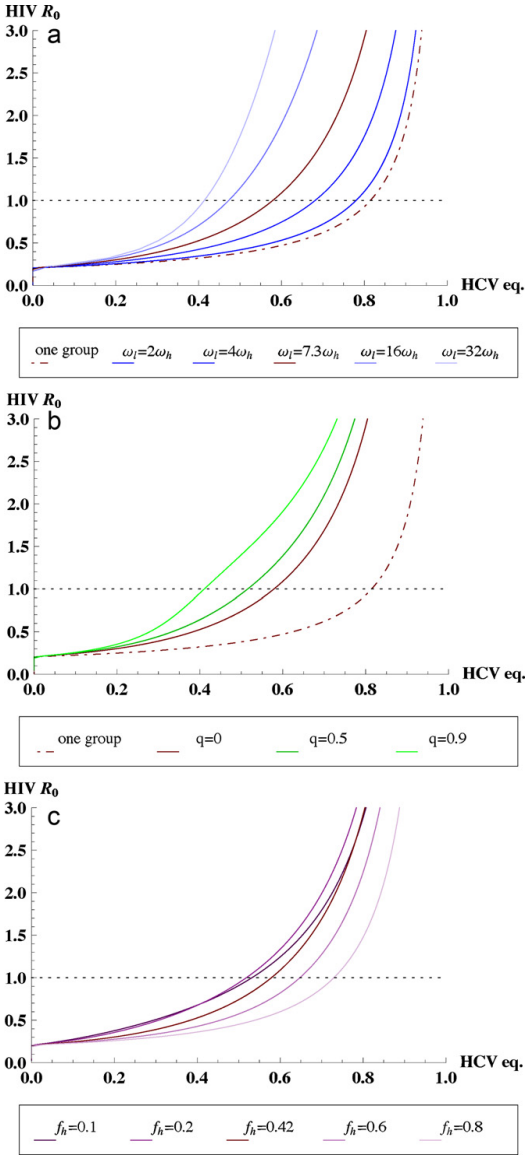

Fig. 3. The basic reproduction number R_0 for HIV plotted against HCV equilibrium prevalence, obtained by varying the average risk within the population. (a) Influence of risk heterogeneity as described by the ratio of syringes shared by high risk IDU to syringes shared by low risk IDU ω_h/ω_l. (b) Influence of q, which describes the fraction of syringes shared within risk groups. (c) Influence of the fraction of high risk takers f_h within the population. When not varied, the number of syringes shared by high risk taking IDU ω_h equals 7.3 times the number of syringes shared by low risk taking IDU ω_l, the fraction of IDU with high risk $f_l = 0.42$, and there is proportionate mixing between risk groups, $q = 0$.

The presence of HIV will influence the equilibrium HCV prevalence in two ways. The direct influence of HIV is a lowered HCV clearance rate, but HIV also increases the death rate especially of high risk taking IDU (the rate of leaving the HCV infected compartment, x in Eq. (14), is increased). This last factor outweighs the first

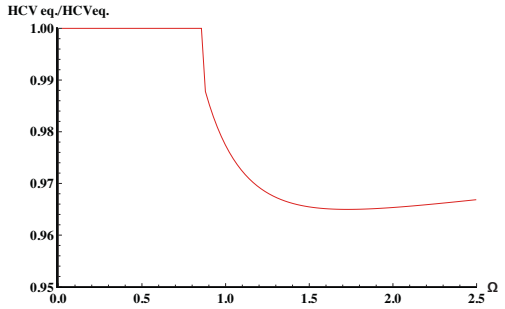

Fig. 4. The ratio of the HCV equilibrium prevalence in the presence of HIV and HCV prevalence in the absence of HIV as a function of the average risk $\overline{\omega}$. Note that the y-axis does not start at 0.

at our chosen parameter values, so that HIV presence lowers HCV equilibrium values, but not by much (see Fig. 4). The impact of HIV on HCV prevalence is largest for intermediate values of $\overline{\omega}$. For large values of $\overline{\omega}$ HCV prevalence is near saturation so that increased death by HIV has little influence.

Without risk heterogeneity, or with risk heterogeneity but without assortative mixing, HIV and HCV prevalence are nearly linearly related (see Fig. 5a). When we add also assortative mixing, HIV prevalence remains lower at low HCV prevalence, as HIV will in this case spread efficiently only within the high risk group (see

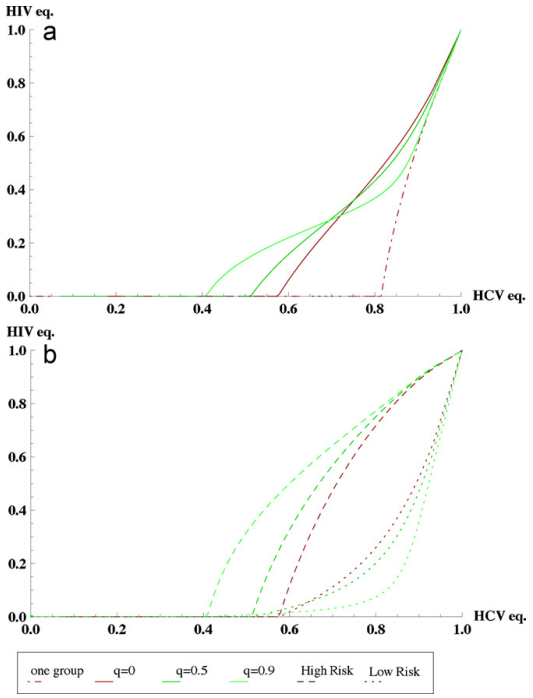

Fig. 5. HIV equilibrium prevalence plotted against HCV equilibrium prevalence obtained by varying the average risk within the population. a) Influence of q, the fraction of syringes preferentially shared within risk groups. b) HIV prevalence is shown separately for the high (dashed) and low (dotted) risk subgroups. For all parameter values, see Table 1.

Fig. 5b). This picture does not change qualitatively if we increase heterogeneity by increasing the number of risk behaviour subgroups to three (results not shown).

Discussion

To summarise, we have analysed the relationship between HIV and HCV in a population of injecting drug users using a mathematical model. The aim was to help answer the question whether HCV prevalence can be used as an indicator of the risk of HIV invasion into an HIV free population. HCV and HIV are both spread through the risk behaviour of sharing of used syringes. However, as we have shown, the distribution of risk within the population and the pattern of mixing determine the relationship between HCV and HIV prevalence. With greater risk heterogeneity HIV is able to spread at lower HCV equilibrium levels. Assortative mixing amongst risk groups enhances this effect.

In their ecological study, Vickerman et al. (2010) found a threshold at around 30% HCV prevalence below which HIV was absent. Using data from the Amsterdam cohort study to inform a model with two risk groups and proportionate mixing, we find that the basic reproduction number R_0 for HIV crosses the threshold of 1 at about 60% HCV equilibrium prevalence. However, for higher levels of risk heterogeneity, or in a population with assortative mixing, the HCV prevalence at which HIV can invade is lowered and approaches values as were observed in Vickerman et al. (2010). Data from 20 Italian regions show a picture qualitatively similar to that shown by Vickerman (Del Fava et al., 2011). The HCV threshold below which HIV is absent seems somewhat higher in this dataset however, perhaps indicating less heterogeneous populations.

Vickerman et al. also note that above threshold, increase of HIV with HCV prevalence is about linear albeit with much variability. However, their linear regression predicts around 30% HIV at a HCV prevalence above 90%, whilst in our model with proportionate mixing both infections increase to very high prevalence levels. This may be an indication for risk heterogeneity with strong assortative mixing, which causes a lower increase in HIV with HCV at the lower risk range (see Fig. 5).

There are some indications that HIV increases HCV viral load, so that HCV infectivity may be increased by co-infection with HIV, and presence of HIV in a population will increase prevalence of HCV (Vickerman et al., 2009). This would also result in HIV prevalence increasing less strongly with HCV at the lower risk range (see Appendix B). However, as this relationship does not seem to be linear as observed in the data, we conclude that other factors better explain the co-occurrence of HCV and HIV as seen in Vickerman et al. (2010). One possible explanation that is supported by our model is the assumption of strong assortative mixing amongst risk groups.

Comparison between our model results and data is limited in several ways. In our analysis we assume either that HCV is in equilibrium with HIV not yet introduced, or that HCV and HIV are both in equilibrium. Populations in reality may be in any stage of the epidemics, which could be the cause of much of the variation between populations found by Vickerman et al. Also, comparison of our results with data is limited by the uncertainty of the parameter values. In particular, for the infectiousness of HCV a wide range of values is reported in the literature. HCV infectiousness relative to HIV infectiousness is a very important determinant of the HCV level at which HIV can invade. Lowering HCV infectiousness p lowers the HCV prevalence at which invasion of HIV is possible (results not shown).

We do not take sexual transmission into account, which would increase HIV prevalence compared to HCV prevalence, as HIV is spread more easily sexually than HCV. However, for IDU the risk of sexual transmission of HIV is generally much lower than the risk of transmission via blood–blood contact, so we did not consider it here. We do not include treatment in our model. The reason is that the data in Vickerman et al. (2010) that we use for comparison include many older data sets from the time period before treatment was applied on a larger scale. But also in the newer data sets we do not expect treatment to have much effect, because it takes a long time before treatment takes effect on prevalence. Including HIV treatment will lower HIV invasion risk, but does not alter our results qualitatively (see Appendix C).

Reliable quantitative data on syringe sharing is rare. Here we analysed risk behaviour data from the Amsterdam Cohort Studies amongst drug users using categorised answers to the question "when did you last use a borrowed syringe". Due to under-reporting of risk behaviour, we use this data for the analysis of heterogeneity in risk behaviour rather than for absolute risk estimates. Our method of fitting risk behaviour into subgroups could in theory be used for a large number of subgroups, or even a continuous distribution. However, that would require more detailed data.

Taking into account the risk distribution within a population could enhance the effectiveness of harm reduction policy. For example, targeting only the highest risk individuals may be sufficient to lower the basic reproduction number of HIV to below 1, or advising low risk takers to avoid sharing especially with high risk takers (more assortative mixing) may lower the HCV equilibrium. Unfortunately, as lowering HIV prevalence in our model does not necessarily also lower HCV prevalence, the best strategies for reducing HIV and HCV disease prevalence may differ.

For a better understanding of risk heterogeneity and how this differs between populations, other data sets should be analysed. For example data on social network characteristics could inform our modelling further, if from this data we can distinguish different risk types and the reality of assortative mixing (Latkin et al., 2011). Other population factors may also influence the relationship between HCV and HIV, such as assortative mixing by injecting duration (Miller et al., 2003).

Reversing the direction of inference, HIV to HCV prevalence at equilibrium can be used to draw conclusions about the risk behaviour distribution. However, the ratio of HIV to HCV prevalence is dependent on all model parameters together, so that it does not provide much specific information about the underlying risk distribution (i.e. only one risk distribution parameter can be fitted to this one population data point).

In conclusion, both HCV and HIV are transmitted amongst injecting drug users by the sharing of contaminated syringes. Clearly, prevalence of HCV is related to the risk for injection-related spread of HIV. As HCV is more infectious, a threshold HCV equilibrium value exists below which HIV cannot establish itself in the population. This threshold value is likely influenced by population risk heterogeneity and mixing by risk behaviour. Therefore, information on heterogeneity in risk behaviour is required to assess the risk that HIV can establish itself and persist at observed levels of HCV prevalence.

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Appendix A. Estimating risk parameters from sharing data from the Amsterdam Cohort Studies

Introduction

Risk behaviour in our model is defined as the rate of borrowing syringes from other drug users. We obtained data on risk behaviour from the Amsterdam Cohort Studies (ACS) amongst drug users (http://www.amsterdamcohortstudies.org/menu/reports/ACSoverview2006.pdf). This open cohort study was started in 1985. Individual (injecting) drug users have been interviewed using a standardised questionnaire in principle every four months (six months since January 2003, but many return more irregularly). Participants receive a small monetary compensation. Recruitment took place at methadone outposts, the weekly STD-clinic for drug-using prostitutes and by word of mouth (van den Hoek et al., 1988).

Comparing our model with data from Amsterdam is complicated by the fact that amongst Amsterdam IDU, prevalence of both HCV and HIV have declined, at least partially due to decline in risk behaviour (Matser et al., 2005). Within the ACS, prevalence of HIV peaked in 1990 at about 35%, and declined to about 20% by 2005. For HCV there is information on HCV antibody status, that is information on ever having been infected rather than current infection. As some individuals have cleared the disease, this means an overestimation of HCV prevalence. The prevalence of HCV antibodies was about 90% in 1990, and has declined to about 83% in 2005.

In order to account for temporal trends in risk behaviour, in our analysis we split the ACS data into the time periods before 1991 and after 1991. Ideally we would like to take shorter time periods, however, sample sizes then become too small for properly fitting our model of borrowing rates.

Within the standard questionnaire of the ACS IDU were asked when they had last borrowed a syringe from another IDU. Answers were possible in 6 categories; either today or yesterday (a_1), within the last week (a_2), within the last month (a_3), within the past half year (a_4), longer ago (a_5), or not since the last interview (at first visit, not within the last 6 months) (a_0). In total there were 1007 answers to the question on borrowing (excluding the "never" answer), 266 within the time period 1986–1991 and 741 in 1991–2005.

Data collected with questionnaires have been shown to underestimate risk behaviour due to socially desirable answering. This is supported by the fact that drug users denying ever injecting drugs still have much higher risk for HCV compared to non drug users (van den Berg et al., 2009). In fact, amongst IDU who indicate recent injecting, the no risk answer, a_0, is given in 86% of cases. We consider this answer least reliable, and therefore do not include it in our analysis.

A model of time since last borrowing

For the subgroups used in our epidemic model, we translate the information on time intervals since last borrowing into borrowing rates. This is done by fitting the sharing rates model to the ACS data by maximum likelihood methods. Note that a population may be homogeneous in that all individuals have the same borrowing probability per unit of time, but that in this case we still expect a distribution of times since last borrowing purely by chance. As before f_j represents the fraction of IDU within a risk group, but we now define IDU to have probability r_j per day to borrow a syringe. Within a group the expected fraction of IDU having borrowed a syringe within the last n_w days but not within the last n_v days is given as $(1-r_j)^{n_v}-(1-r_j)^{n_w}$. Interval limits corresponding to the answers a_1 to a_5 are taken as $n_w = 2$ and $n_v = 0$, $n_w = 7$ and $n_v = 2$, $n_w = 30$ and $n_v = 7$, $n_w = 157$ and $n_v = 30$, and $n_w = \infty$ and $n_v = 157$, respectively.

Adding the probabilities for all subgroups we can define the probability of answer a_j as:

$$\underset{a_j}{P}(r_i, f_i) = \sum_{i=1}^{k} f_i((1-r_i)^{n_v} - (1-r_i)^{n_w})$$

with A_j the number of answers a_j in our data, the likelihood (L) of the data under model assumptions is given as:

$$L(r_j, f_j, A_j) = \sum_{j=1}^{5} \underset{a_j}{P}^{A_j}$$

The model parameters are estimated by maximising this likelihood.

We fit and compare three models: a one group model, a two group model, and a three group model. In a model of three groups there are five parameters, three of syringes shared, and two of relative group sizes. Since the data only contains four degrees of freedom (five answer categories), fitting a model with more than two groups would be overfitting to the data. However, we still aim for a unique three-group model solution by defining relative group sizes, and then fit only the three parameters describing syringe borrowing within these groups.

The fitted probability per day can be interpreted as a rate per day, re-calculable to a rate per month for use in our transmission model. In our estimation we assume that IDU borrow at most one syringe per day, therefore a rate of 30 syringes per month is an upper bound. However, as our best fit estimates do not approach this upper bound (see results), this limitation is unlikely to bias our results.

Results of the ACS risk behaviour analysis

Reported risk behaviour has declined over time (see Figs. A1 and A2). For both periods the Bayesian Information Criterion (BIC) for the one group model is much larger than the BIC for the two group model (see Table 2). We conclude that the data gives strong evidence for heterogeneity in risk behaviour. Including three groups, and attempts at fitting a saturated (four parameter) three or four-group model, did not improve the fit. We therefore conclude that the data is not detailed enough to parameterise a model with more than two groups.

Focussing on the two group models the predicted risk has declined for both groups, leaving heterogeneity in risk as measured by high relative to low risk almost unchanged (f_h/f_l =7.42 before and f_h/f_l = 7.32 after 1991 respectively). However, after 1991 a slightly larger part of the population is placed in the low risk subgroup. Where the one group model risk estimates predict that HIV is unable to spread, the two risk model results are comparable with actual prevalences of both HCV and HIV.

As mentioned, 86% of IDU stated that they had not borrowed syringes since their last visit. Clearly, if 86% did not take any risk, disease prevalences could never be above 14%, and we conclude that these statements are highly unreliable. However, if some IDU answer the question truthfully, we have overestimated the true risk, and underestimated the risk heterogeneity.

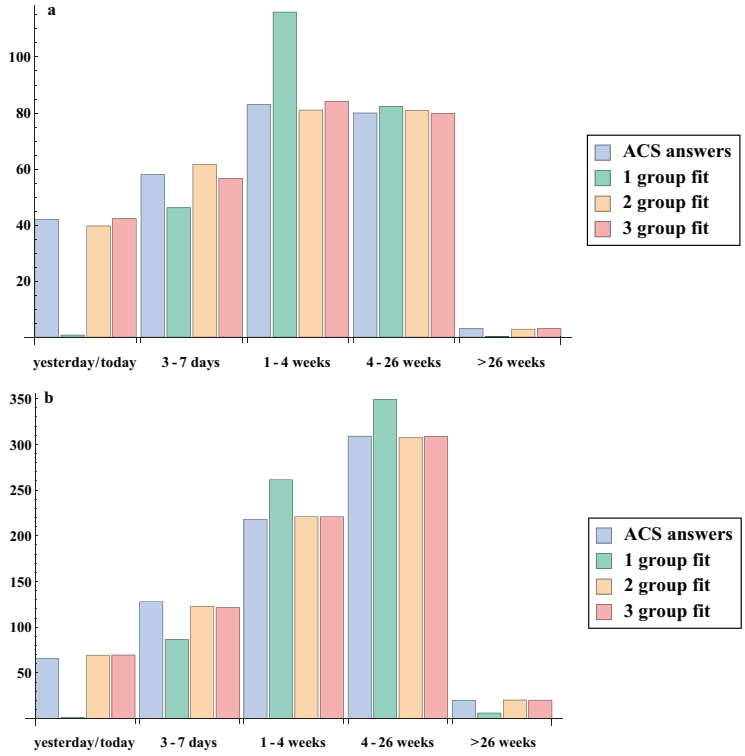

Fig. A1. Number of times answers are given in the five categories to the ACS questionnaire question "when did you last borrow a syringe", and the predicted answers from our best fitting models (see text). (a) 1986–1991 and (b) 1991–2005.

Table 2
Estimated risk parameters from sharing data from the Amsterdam Cohort Studies (ACS) amongst drug users.

Model	Group fractions f_j	Sharing rates ω_j	av. risk	Log likelihood	BIC	HCV eq.	Ever-HCV eq.	HIV eq.
Onegroup < 1991	1.00	1.23	1.23	-172.8	351	0.78	0.83	0.00
Two groups < 1991	0.58, 0.42	0.65, 4.76	2.38	−10.0	37	0.76	0.81	0.39
Threegroups < 1991	0.50, 0.25, 0.25	0.62, 2.06, 7.03	2.58	−9.8	36	0.77	–	0.40
Onegroup > 1991	1.00	0.78	0.78	−268.9	544	0.65	0.72	0.00
Twogroups > 1991	0.71, 0.29	0.53, 3.93	1.52	−12.2	44	0.69	0.74	0.24
Threegroups > 1991	0.50, 0.25, 0.25	0.49, 0.73, 4.24	1.49	−12.2	44	0.68	–	0.24

Estimates are compared using the Bayesian Information Criterion (BIC). Average risk behaviour per IDU is calculated as $\sum_{j=1}^{k} f_j \omega_j$. HCV and HIV prevalences are calculated by the HIV and HCV dynamics model of our main article. Additionally, ever-HCV prevalence is calculated by extending our model with separate compartments for those who have cleared HCV. Within the ACS ever-HCV prevalence has declined from ∼90% in 1990 to ∼83% in 2005, and HIV peaked at ∼35% in 1990 and declined to ∼20% in 2005.

Appendix B. Increased HCV infectivity for HIV co-infecteds

There are some indications that HIV increases HCV viral load, so that HCV infectivity may be increased by co-infection with HIV, changing the HCV HIV relationship (Vickerman et al., 2009). Here we include this fact in our model, by redefining λ_j. Per subgroup, the proportion of IDU HCV positive but HIV acute or negative $\pi_j^- = (I_j^S + I_j^I + C_j^S + C_j^I)/(S_j^S + S_j^I + S_j^C + I_j^S + I_j^I + I_j^C + C_j^S + C_j^I + C_j^C)$, so that the chance that a randomly borrowed syringe carries HCV from a HIV acute or negative individual $m^- = (\sum_{j=1}^{k} \omega_j f_j \pi_j^-)/(\sum_{j=1}^{k} \omega_j f_j)$. The proportion of IDU HCV positive and HIV chronic $\pi_j^+ = (I_j^C + C_j^C)/(S_j^S + S_j^I + S_j^C + I_j^S + I_j^I + I_j^C + C_j^S + C_j^I + C_j^C)$, so that the chance that a randomly borrowed syringe carries HCV from an HIV chronic individual $m^+ = (\sum_{j=1}^{k} \omega_j f_j \pi_j^+)/(\sum_{j=1}^{k} \omega_j f_j)$, and the total force of infection for HCV becomes:

$$\lambda_j = \omega_j p(q\pi_j + (1-q)m^-) + \omega_j pY(q\pi_j + (1-q)m^+) \quad (19)$$

In which Y represents the HCV infectivity of IDU with chronic HIV relative to HCV infectivity of HIV negative IDU.

If HIV co-infection increases infectivity of HCV, an HIV infected individual will more often become co-infected by HCV, so that R_0 of HIV is increased. Therefore the threshold HCV prevalence at which HIV can persistently spread is increased. However, due to the HCV induced death rate being relatively small, this effect is only very slight. Beyond this threshold, HIV prevalence increases less strongly with HCV prevalence compared to our model where HIV does not affect HCV infectivity (see Fig. A2). However,

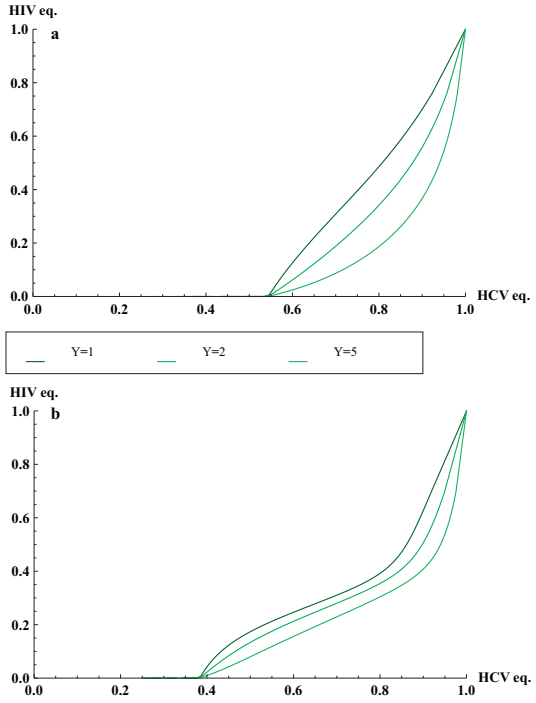

Fig. A2. HIV equilibrium prevalence over HCV equilibrium prevalence, obtained by varying the average risk in the population, as influenced by Y, the HCV infectivity of IDU with chronic HIV relative to HCV infectivity of HIV negative IDU. (a) $q = 0$, proportionate mixing. (b) $q = 0.9$, strongly assortative mixing. For all other parameter values, see Table 2.

without assortative mixing, this increase resembles exponential rather than linear increase. We therefore conclude that the assumption of strong assortative mixing better explains the co-occurrence of HCV and HIV described by Vickerman et al. (2010).

Appendix C. Effect of treatment on the relationship between HCV and HIV prevalence

In our main article we have ignored treatment for HIV and HCV. Our reason for doing so is that we compare our results with data from the review by Vickerman et al., and as this review includes many older data sets, treatment should not have had time to influence prevalences much (Vickerman et al., 2010). HIV treatment has been available since about 1996, however, HCV treatment amongst IDU is only very recent. With rates of treatment success and re-infection not yet available, the possible future impact of HCV treatment is still uncertain.

Here we include highly active antiretroviral treatment (HAART) in our model, but simplify by assuming no acutely, and all chronically HIV infected IDU to receive treatment. We lower the HIV induced death rate to $\mu^H = 0.0016$ (Smit et al., 2006). This by itself would lead to a slight increase in HIV compared to HCV prevalence (results not shown). However, a far larger impact on HIV is caused by the fact that HAART treatment lowers infectiousness about tenfold (Attia et al., 2009). Therefore, our model predicts that the HCV prevalence at which HIV can invade is increased by HIV treatment (see Fig. A1). However, a more quantitative analysis of this effect would depend on the actual HAART uptake amongst HIV

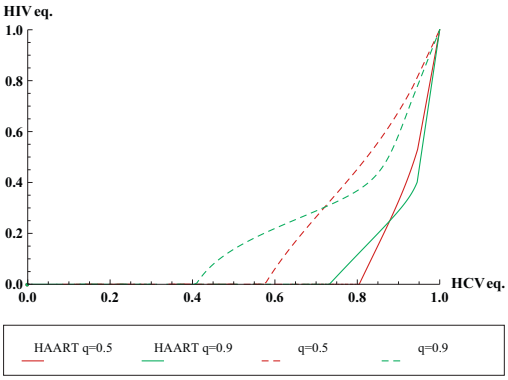

Fig. A3. HIV equilibrium prevalence over HCV equilibrium prevalence, obtained by varying the average risk in the population, with HAART treatment for HIV positive IDU. HIV prevalence without HAART, dashed lines, is shown for ease of comparison. We assume all chronically HIV infected individuals are on full HAART treatment. The death rate for chronically HIV-infected IDU is lowered to $\mu^H = 0.0016$, and infectiousness within the chronic HIV stage is lowered to $p^{H_C} = 0.0008$ per syringe. For all other parameter values see Table 2.

positive IDU, as well as other behavioural factors. For example, HIV treatment might be associated with an individual's chance to stop injecting drug use (see Fig. A3).

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CHAPTER 3

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

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

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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.

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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

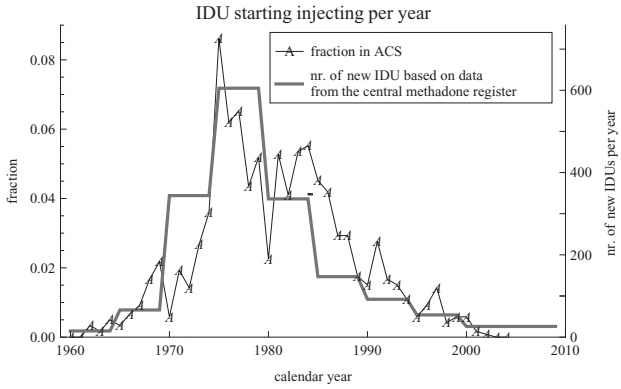


Figure 1 The fraction of all Amsterdam Cohort Study (ACS) participants who started injecting within a particular calendar year compared to the estimated inflow of new injecting drug users (IDU) per year based on data from the central methadone register of Amsterdam (from [16]). This last information 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

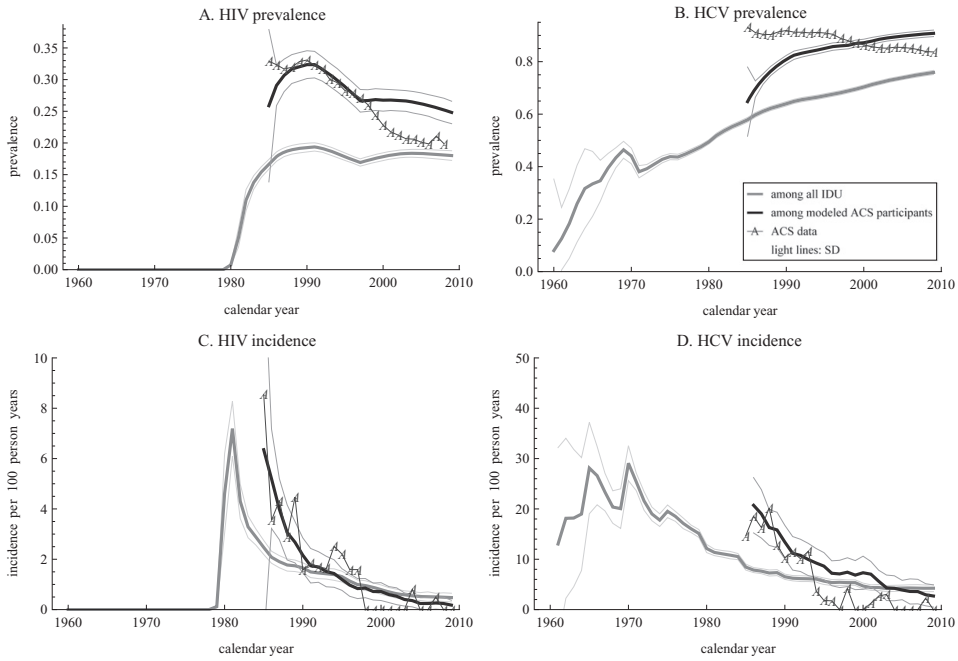


Figure 2 Infection and population dynamics in the baseline scenario from 1960 to 2010. (a) HIV prevalence. (b) Hepatitis C virus (HCV) prevalence (defined by the presence of HCV antibodies; it does not distinguish chronic from spontaneously cleared infection: see text). (c) HIV incidence. (d) HCV incidence. 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

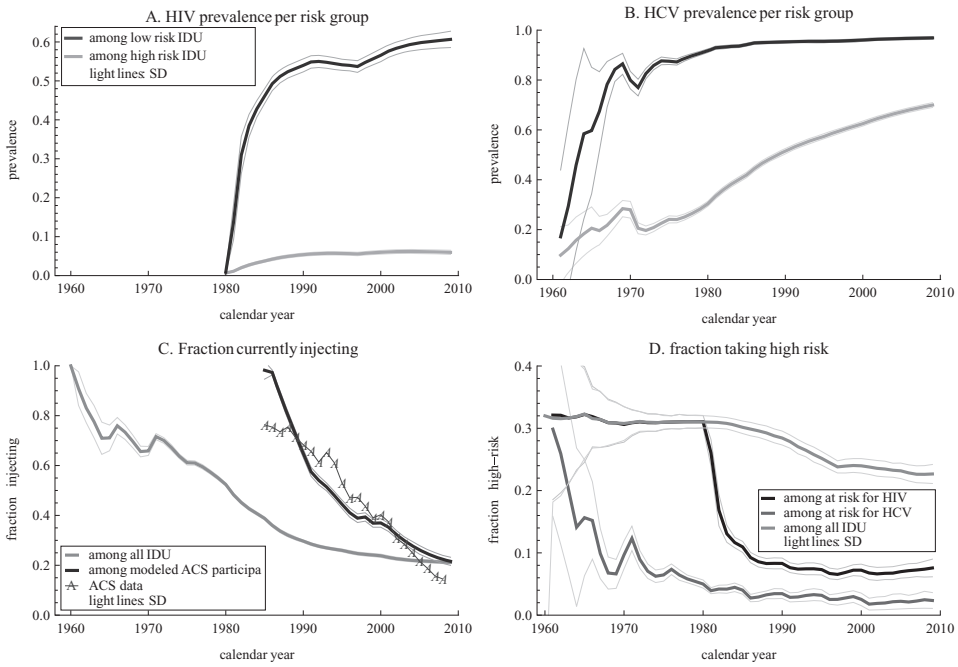


Figure 3 (a) HIV prevalence for low- and high-risk injecting drug users (IDU). (b) Hepatitis C virus (HCV) prevalence for low- and high-risk IDU. (c) Fraction of IDU currently injecting. (d) Fraction of high-risk currently injecting IDU, separately for those at risk for HIV (HIV-negative) and those at 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).

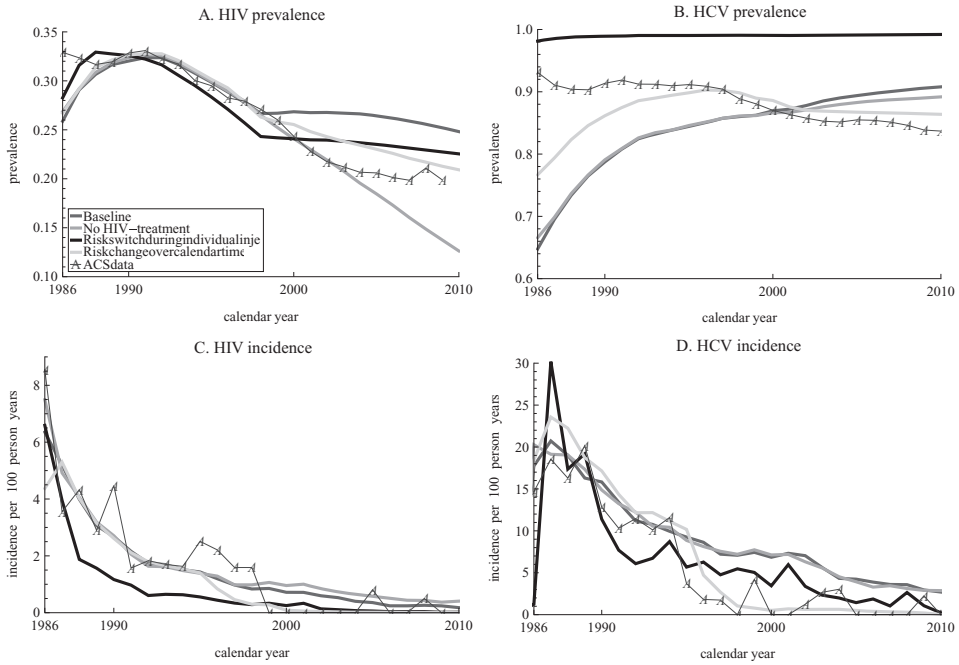
Because HIV-related mortality was concentrated within the high-risk group, population risk decreased. Not only did IDU remain at risk for disease, borrowing fewer syringes on average, when they borrowed syringes these were less likely to come from a high-risk-taking/HIV-infected IDU. This enabled a strong 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

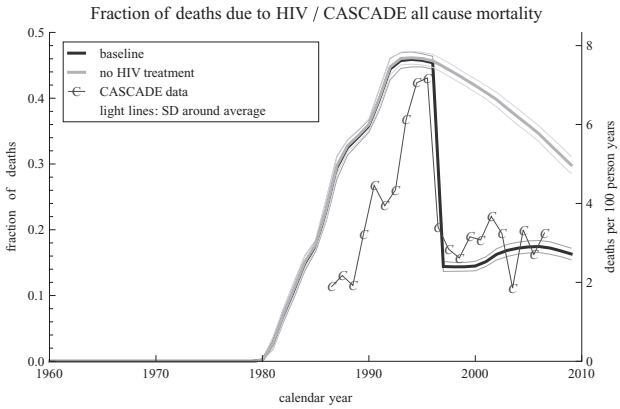


Figure 5 Fraction of overall mortality in the model which is due to HIV, and the overall mortality rate in HIV-infected injecting drug users (IDU) from the CASCADE (Concerted Action on SeroConversion to AIDS and Death in Europe) Collaboration. At the peak of HIV prevalence, around 1990, almost half of 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

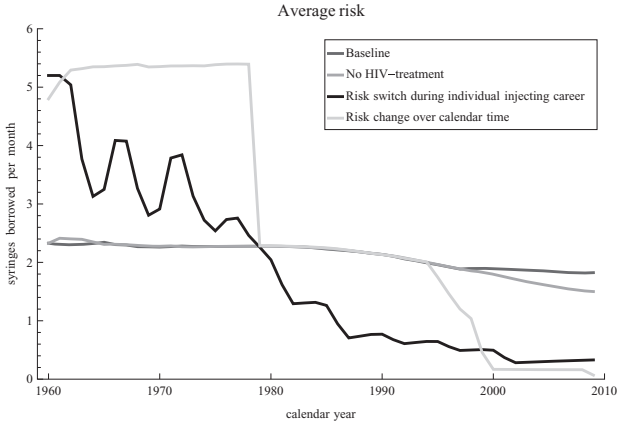


Figure 6 Average risk [number of syringes exchanged per month per injecting drug user (IDU)] in the different scenarios over time. In the baseline scenario and the no HIV treatment scenario, risk declined due to higher HIV-induced mortality among higher-risk IDU. In the risk change over calendar time 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.

Acknowledgements

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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).

Supplementary to "Decline in incidence of HIV and Hepatitis C virus infection among injecting drug users in Amsterdam; evidence for harm reduction?" Anneke S. de Vos, Jannie .J. van der Helm, Amy Matser, Maria Prins, Mirjam E.E. Kretzschmar.

Model formulation

We implemented an individual-based model that, for each individual *i*, kept track of injecting status, infection status, age and time since HIV infection. The model used discrete time steps of one month and all individual states were updated every month *t*. Age at first injecting was drawn from a normal distribution (mean 22.3, variance 6.4 years), and rounded to months. Every month the time variables age, duration of injecting, and time since HIV seroconversion, were updated.

Discrete parameters were defined by comparing status probabilities with randomly drawn real numbers in the interval [0, 1]. For example, to determine the risk type of a new IDU at model entrance, a random number was drawn. When the random number exceeded a parameter *F*, the IDU had risk type 'high' else he/she had risk type 'low'. Individuals currently injecting had a probability each month to cease injecting, those who stopped had a chance to relapse to injecting behaviour. For those not currently injecting individual risk R_i in syringes borrowed per month was 0, for those injecting the borrowing rate depended on their risk-type. The individual chance of acquiring infection, λ_i, depended on R_i and on the infection status of the IDU borrowed from:

$$\lambda_i^{HIV} = 1 - (1 - p^a)^{s_i^a} (1 - p^c)^{s_i^c} (1 - p^{cc})^{s_i^{cc}}$$

Where p^a, p^c and p^{cc} were the probabilities of acquiring infection per syringe borrowed from an acutely, a chronically, or a chronically but cART using HIV-infected IDU respectively, and s_i^a, s_i^c and s_i^{cc} denote the expected numbers of syringes borrowed from these types of IDU. Parameter *q* denotes the fraction of syringes preferentially borrowed from IDU with similar risk type as the borrower, the remaining fraction of borrowing events was random:

$$s_i^a = R_i((1-q) f_a + q f_{ai})$$

$$s_i^c = R_i((1-q) f_c + q f_{ci})$$

$$s_i^{cc} = R_i((1-q) f_{cc} + q f_{cci})$$

f_a represents the fraction of all borrowed syringes in the population that were lent out after use by an acute HIV-infected individual. We assumed that an individual's probability of borrowing syringes equalled their probability of lending syringes to others.

Therefore f_a is obtained by summing the risk variable R_i of the acutely HIV-infected IDU and dividing the result by the summed R_i for all IDU, i.e.

$$\frac{\sum R_i((\text{If HIV} + \& \text{ time since HIV infection} \le 3 \text{ months})}{\sum R_i}$$

f_{ai} denoted the fraction of syringes carrying infection from acute infected IDU only within the subpopulation of IDU of similar risk type. Analogously, f_c equalled the total of syringes that were lent out by all chronic HIV-infected IDU divided by the total number of syringes lent out by IDU. i.e.

$$\frac{\sum R_i((\text{If HIV} + \& \text{ time since HIV infection} > 3 \text{ months})}{\sum R_i}$$

f_c therefore represents the fraction of all borrowed syringes that were lent out after use by chronic HIV-infected individuals in the total population. For f_{ci} we totalled the number of syringes lent out by chronic HIV-infected IDU within the subpopulation of IDU with the same risk type as individual *i*, and divided this by the total number of syringes lent out within this subpopulation. f_{cc} gave the fraction of all syringes lent out after use by a chronic infected IDU on cART treatment, f_{cci} the same within the risk subpopulation of individual i.

For HCV we distinguished p^{an}, p^{cn}, p^{ah}, and p^{ch}, the probabilities of acquiring HCV infection per syringe borrowed from an acutely HCV but not HIV, chronically HCV but not HIV, acutely HCV and HIV, and chronically HCV and HIV-infected IDU respectively. s_i^{an}, s_i^{cn}, s_i^{ah} and s_i^{ch} denote the expected numbers of syringes borrowed from these types of IDU. These depended on the fraction of syringes lent out after use by the respective types of IDU:

$$\lambda_i^{HCV} = 1 - (1 - p^{an})^{s_i^{an}} (1 - p^{cn})^{s_i^{cn}} (1 - p^{ah})^{s_i^{ah}} (1 - p^{ch})^{s_i^{ch}}$$

$$s_i^{an} = R_i((1-q) f_{an} + q f_{ani})$$

$$s_i^{cn} = R_i((1-q) f_{cn} + q f_{cni})$$

$$s_i^{ah} = R_i((1-q) f_{ah} + q f_{ahi})$$

$$s_i^{ch} = R_i((1-q) f_{ch} + q f_{chi})$$

At 6 months of HCV infection individuals had a probability of 0.25 to clear HCV infection, unless co-infected by HIV, in which case the probability to clear was lowered to 0.15. Within the ACS HCV antibody status has been tested for, which does not distinguish persisting from cleared HCV infections. The model therefore also recorded if IDU had ever been infected by HCV, and the figures show prevalence of this ever-HCV variable rather than the current HCV status of IDU.

From 1986 onwards, at the beginning of each year, randomly chosen but actively injecting IDU were enrolled within a modeled ACS, the modeled numbers recruited per year equaling actual numbers recruited. Once he/she was participating, an IDU remained participating until removal. The removal-rate for all IDU included a probability to move out of Amsterdam and a mortality-rate, this last depending on individual age and disease status, including time since HIV seroconversion (see the parameter section).

For the scenario with risk switching during individual injecting time, the number of syringes borrowed and lent out by individuals depended on time since first injecting only (there was no risk heterogeneity between individuals in this scenario), i.e. If age < x months risk type was high, else it was low, which determined together with the currently injecting status the risk R_i. For this scenario we simplified by setting $q = 0$ (all borrowing was random).

The model was implemented in Mathematica version 7.0. Per simulated scenario one hundred model runs were performed. Figures give the average and standard deviation of these one hundred simulations. The fit of the scenarios was compared by calculating the squared residuals with the yearly incidence and prevalence measures from the ACS.

Supplementary tables and figures:

Age at HIV seroconversion	<1997, years since HIV seroconversion:				>1997, years since HIV seroconversion:			
	0-2	2-5	5-10	>10	0-5	5-10	10-15	>15
<20	-0.0004=0	0.0007	0.0026	0.0084	0.0000	0.0008	0.0012	0.0011
20-24	-0.0006=0	0.0016	0.0036	0.0081	0.0007	0.0010	0.0013	0.0016
25-29	0.0007	0.0020	0.0068	0.0163	0.0003	0.0012	0.0020	0.0038
30-34	0.0025	0.0019	0.0084	0.0224	0.0010	0.0020	0.0082	0.0035
>35	0.0039	0.0078	0.0100	0.0224	0.0015	0.0032	0.0124	0.0108

Table S1. Additional HIV-induced mortality, based on data from the CASCADE Collaboration. From the mortality rates per group we have subtracted non-HIV-induced background mortality, the age-specific HIV-negative IDU mortality estimated from the ACS.

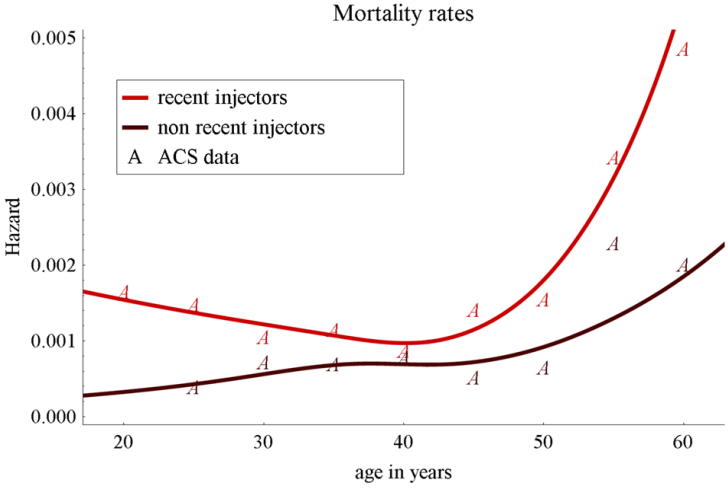

Fig S1. Death rates per month by age, separately for recent injectors and non-recent injectors. Recent injecting was defined as having reported injecting episodes for a period between interviews (in response to the question "have you injected since your last ACS visit?"). Lines give the best fit for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

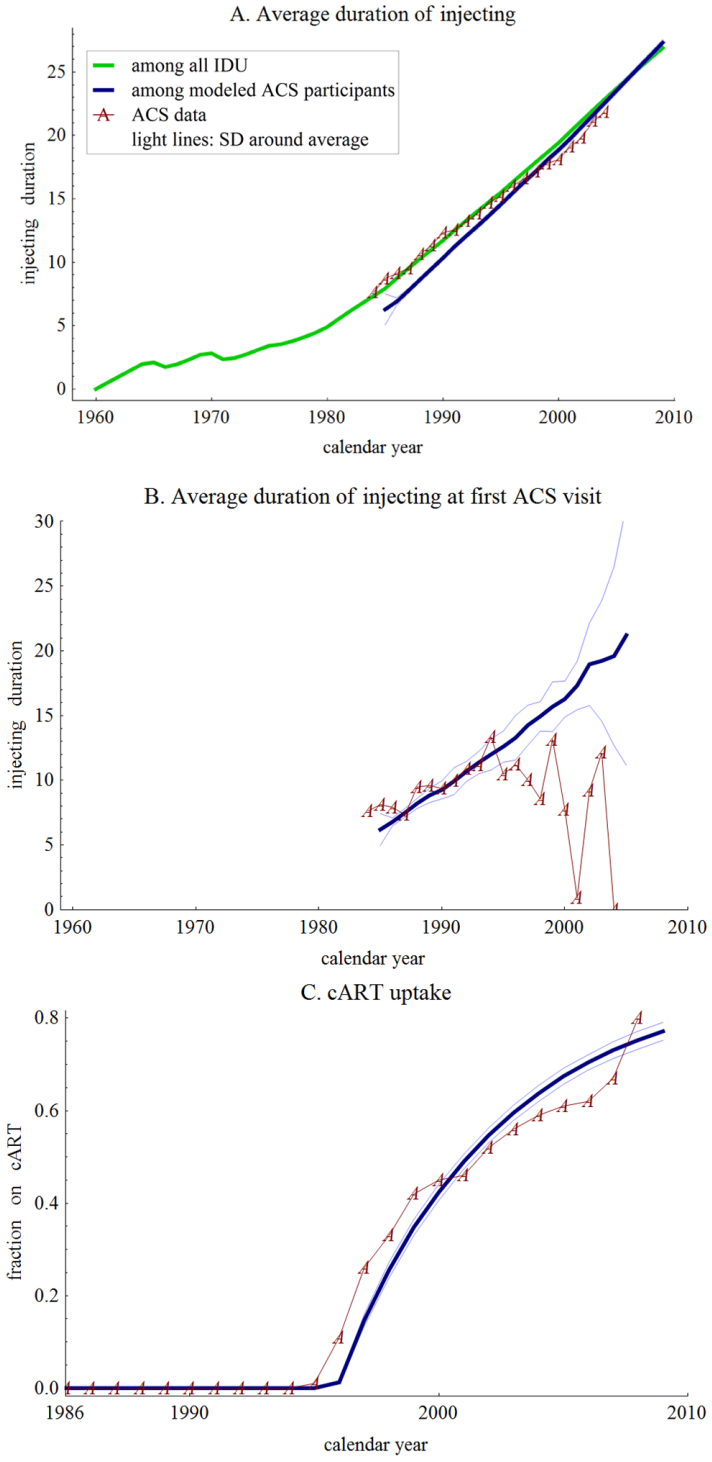

Figure S2. A) Average duration of injecting. B) Average duration of injecting at first ACS visit. C) cART uptake. A stop-injecting-rate of 0.016 combined with a relapse-rate of 0.04 gave a good fit to the variables of injecting duration, as well as to the fraction of IDU currently injecting within the ACS (main text figure 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 lower modeled 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-seroconverison dates, cART was defined as at least three antiretroviral drug types. A 0.0125 probability per month from 1996 onwards to start cART gave a good fit to this data. Baseline model parameters (see table 1). The average of one hundred simulations is shown (plus or minus one standard deviation).

CHAPTER 4

Treatment as prevention among injecting drug users; extrapolating from the Amsterdam cohort study

Treatment as prevention among injecting drug users; extrapolating from the Amsterdam cohort study

Anneke S. de Vos[a], Maria Prins[b,c], Roel A. Coutinho[a,d], Jannie J. van der Helm[b] and Mirjam E.E. Kretzschmar[a,d]

Objective: To determine the potential of treatment as prevention for reducing HIV incidence among injecting drug users (IDU).

Methods: Transmission dynamics of HIV as influenced by cART uptake and demographic changes were studied using an individual-based model. Parameters were based on data of the Amsterdam Cohort Study, and counterfactual treatment scenarios were examined for this city. Demography of the modeled population was also varied to allow for more general conclusions.

Results: We estimated that over the complete HIV epidemic among IDU in Amsterdam the historic use of cART has led to only 2% less incidence. As individuals were treated from low $CD4^+$ cell counts, their decreased infectiousness was offset by increased infectious lifetime. Large reduction in incidence could result from a test and immediate treat strategy, with elimination of HIV occurring when the average time from infection to starting treatment was less than 2 months. However, substantial proportions of new infections were prevented only if the test and treat intervention was implemented within the first few years after HIV-epidemic onset, especially for a declining IDU population. Ignoring heterogeneity in risk-behavior led to overly optimistic expectations of the prevention effects of treatment. In general, treatment led to much greater reduction in incidence compared with stopping HIV-infected IDU from lending out syringes.

Conclusion: A test and immediate treat strategy for HIV among IDU could lead to great reductions in incidence. To fully eliminate the spread of HIV, treatment as prevention should be combined with other interventions, with behavioral intervention directed at those not yet HIV infected.

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Keywords: HIV, injecting drug use, risk heterogeneity, test and treat, treatment as prevention

Introduction

Much attention has recently been given to the concept of treatment as prevention (TasP) [1–3]. As combination antiretroviral therapy (cART) lowers viral load, it not only completely changes the prognosis of those infected with HIV, but it also lowers their likelihood of infecting others [4]. From modeling studies describing the sexual spread of HIV, some have even postulated that sufficient treatment uptake would lead to elimination of the virus [5]. Others however have warned against overly optimistic expectations [6].

So far, the possible benefit in lowered HIV incidence of TasP has been less rigorously studied for treatment of injecting drug users (IDU), although IDU represent about 10% of those infected with HIV worldwide [7]. Most studies that model the spread of HIV among IDU have included treatment only of those with low $CD4^+$ cell counts, reflecting the current treatment guidelines

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which are based on health benefits of those treated rather than population benefits [8]. Few studies so far have examined a test and treat strategy among IDU; providing immediate treatment for those testing positive independent of $CD4^+$ cell count [9].

We previously introduced a model of the IDU population in Amsterdam to investigate the possible reasons for the decline in HIV and HCV prevalence and incidence in this city [10]. We found that taking into account the strongly changed demography within the Amsterdam IDU population over the years was of great importance for explaining the observed patterns of disease spread. In particular, strong heterogeneity in risk behavior together with decreasing population size could explain much of the decline in HIV prevalence.

Demographic changes will also strongly impact on the possibility for lowering HIV incidence by uptake of cART. Compared with other populations for which treatment as prevention has been investigated, IDU populations may be less stable; in certain regions of China, Russia and India relatively recently established populations of IDU are found [11], on the contrary, in many parts of Europe injecting drug use is currently in decline [12]. Compared with sexual spread, spread of HIV by use of contaminated injecting equipment is very efficient, so that very high levels of HIV prevalence can occur within IDU populations [7].

cART has been prescribed to IDU in Amsterdam since it first became available from around 1996. Here, we investigate the impact that treatment has likely had within this city using an adapted version of our earlier model. Extrapolating from Amsterdam, we also investigate how a strategy to test and treat IDU would impact on HIV incidence in populations with different demographic developments. For a stable, increasing or decreasing IDU population, we estimate the total incidence over the first 30 years of an HIV epidemic, as influenced by the rate of starting treatment for HIV. We also consider the influence of the elapsed time between the first HIV cases entering the population and the implementation of the test and treat regimen.

Methods

We adapted an individual based model, which was developed to describe demographic changes of both HIV and hepatitis C infection dynamics within the IDU population of Amsterdam [10]. Most demographic parameters for this model were estimated from the Amsterdam Cohort Studies (ACS) among IDU. Recruitment for this study has been ongoing since 1985, and took place at methadone outposts, the weekly STD-clinic for drug-using prostitutes and by word of mouth. In principle every 4–6 months ACS participants were interviewed and provided blood-samples, from which HIV and (retrospectively) HCV-status were determined [13]. Total IDU population size in Amsterdam was based on back calculations from IDU participating in methadone maintenance treatment [14].

Individuals entered the model at the start of their injecting-career. Subsequently, they could stop injecting but also relapse, acquire HIV and move out of Amsterdam or die, depending on their age and injection status, which were updated each month. To allow comparison between our model and the ACS data, we modeled ACS recruitment, thereby creating a model ACS-cohort within the modeled population. Modeled individuals were either high-risk, both borrowing from and lending syringes to many others, or low-risk throughout their injecting-career. Reliable information on risk behavior is very difficult to obtain, not just for IDU in Amsterdam but in general. Therefore, we based the absolute sharing rates, relative size of the behavioral sub-groups, and also an increased likelihood to share with someone of similar risk, on the model fit to ACS data of HIV and HCV prevalence and incidence [10] (as briefly summarized in Appendix Figure 1, http://links.lww.com/QAD/A466). We assumed no change in risk-behavior associated with either HIV-diagnosis or start of treatment [15].

The HIV acute stage was assumed to last 2 months [16], during which infectiousness was 10-fold that of chronic infection [17]. Infectiousness was lowered 90% in either stage by use of cART, based on data from sexual transmission studies [18]. HIV-induced mortality in our model depended on age and time since HIV infection, and is based on IDU-specific data from the CASCADE Collaboration [19]. As most of this data was from hospital cohorts, we assumed that from the broad introduction of cART in 1997 onwards most participants in need of treatment received it. We therefore based mortality of those on cART in our model on this data from 1997. Those not on cART experienced mortality based on the CASCADE data from before 1997.

For our baseline scenario, cART uptake was fit to data on antiretroviral use by the HIV-infected IDU in the ACS. We assumed that those starting treatment remained on treatment. Until recently cART was usually initiated only with the onset of clinical symptoms, or when an individual's $CD4^+$ cell count dropped below 350 cells/μl [20], which approximately corresponds to HIV infection more than 6 year duration [21]. The fit between model and actual cART use was achieved by assuming a 1/96 ($\approx$0.01) probability per month to start cART for all IDU with more than 6 year HIV infection from 1996 onwards. That is, including those never treated, the average individual started cART at 14 years from infection (see Fig. 1).

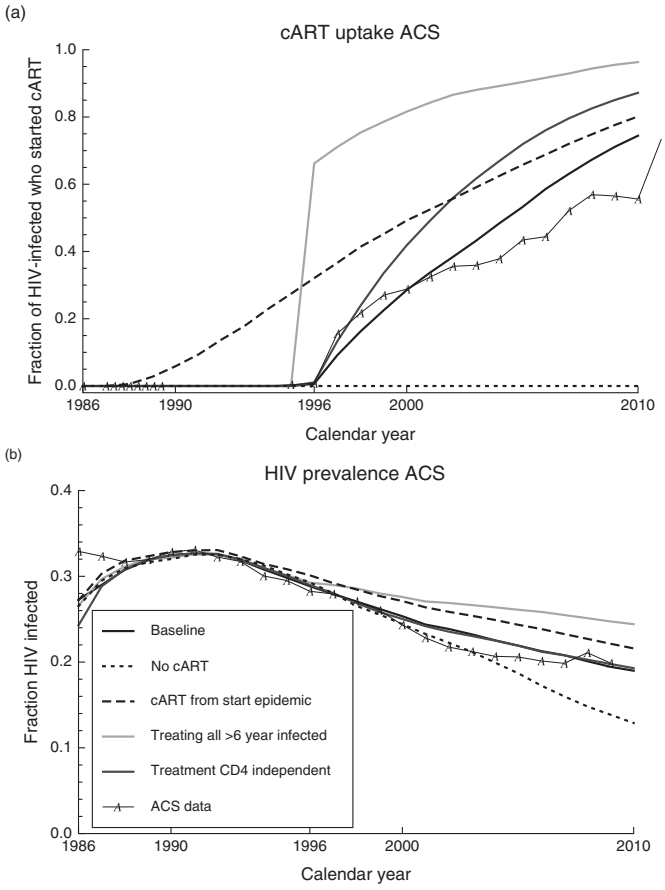

Fig. 1. Combination antiretroviral therapy (cART) uptake (top panel) and HIV prevalence (bottom panel) within the modeled cohort, as compared to data from the actual Amsterdam Cohort Studies (ACS) among injection drug users (IDU).

We considered four counter-factual scenarios for Amsterdam. We modeled cART never having been introduced and cART introduction from the start of the HIV epidemic among IDU in 1980. We also investigated an increased cART uptake rate (from 1996 treatment of all IDU >6 year HIV-infected) and treatment independent of $CD4^+$ cell count (from 1996 a 0.01 monthly starting-rate for all HIV-infected IDU) (Table 1). Note that since cART use was updated at the end of each month, time from infection to lowered infectiousness was at least 1 month for individuals, also in this last scenario.

We then adapted the model demography to investigate benefits of a test and treat strategy for IDU in a more general setting. We first considered a stable IDU population: four new IDU entered each month, resulting in approximately 2000 IDU at equilibrium. We considered an increasing population (with initially 200 IDU) and a decreasing population (with no new IDU entering). We also considered a stable population in which all IDU shared syringes equally. An epidemic was initiated by entering 20 HIV-infected IDU. We determined the cumulative number of infections within the first 30 years of the epidemic, as influenced by the monthly cART starting probability and the time elapsed between the first HIV cases and test and treat implementation.

We additionally investigated the impact of changing behavior of (equivalent to isolating) HIV-infected IDU; in the above described stable population setting, we combined testing and treatment of HIV-infected individuals with assuming that the treated individuals fully ceased all syringe sharing with other IDU.

The model was implemented in Mathematica version 7. To account for the stochastic nature of events in our model, each scenario was repeated 50 times, and results

Table 1. Five different modeled scenarios for the HIV-epidemic among injection drug users in Amsterdam. Based on back calculations from methadone maintenance treatment, a total of 8606 new IDU are included in the model from 1960 to 2010. For each scenario the cumulative number of HIV infections, HIV-related deaths, and person months on combinationantiretroviral therapy are given from the start of the epidemic in 1980 up to 2010, in brackets as compared to baseline.

	Number of infections	HIV-related deaths	Person months on cART
Baseline (fit to data). From 1996, IDU >6 years infected had a monthly 0.01 probability to start cART	2366	1382	44535
No cART	2422 (102%)	1605 (116%)	0 (0%)
cART available from 1980, IDU > 6 years infected had a monthly 0.01 probability to start cART	2309 (98%)	1201 (87%)	95305 (214%)
Treatment uptake rate increased, from 1996, all IDU >6 years infected started cART at 1 month from infection	2219 (94%)	1055 (76%)	119597 (269%)
Treatment $CD4^+$ cell count independent, from 1996, all HIV-infected IDU had a monthly 0.01 probability to start cART	2278 (96%)	1300 (94%)	64561 (145%)

cART, combination antiretroviral therapy; IDU, injection drug users.

were averaged. We considered a decline from the initial 20 prevalent cases at the end of the 30 years in more than 50% of model runs as indicating the eventual elimination of HIV.

Results

Uptake of cART among participants in the ACS was well described by assuming a 0.01 probability of starting cART per month for all IDU HIV-infected more than 6 years (approximating the criterion of a $CD4^+$ cell count < 350 cells/μl) (Fig. 1a). HIV prevalence within the ACS was fit by assuming two risk subgroups of IDU: as those sharing more syringes were infected and died of HIV first, population risk decreased, resulting in a decline in HIV prevalence over time (Fig. 1b). The risk behavior parameters were additionally informed by the HIV and HCV incidence and HCV prevalence data (see Appendix Figure 1, http://links.lww.com/QAD/A466).

In our baseline scenario, with all model parameters as best informed by the data, we estimated that around 2400 of all 8600 ever-IDU in Amsterdam became infected, and 1400 IDU died of HIV from the start of the epidemic up to 2010 (Table 1). To gain insight in the role of cART, we next examined several counter-factual scenarios for Amsterdam. We estimated that had cART not been available, mortality would have been 16% higher, which would have led to a decreased HIV prevalence compared with the baseline prevalence (Fig. 1). Conversely, had cART been available and uptake similar from the start of the HIV epidemic, we estimated that HIV-related mortality would have been 13% less. Although cART lowers infectivity of individuals, the increased survival it enables (resulting in higher HIV-prevalence) has a compensatory effect on incidence: we estimated a 2% decrease in overall incidence only if cART had been available from 1980 compared with its availability from 1996 at baseline.

Similarly, if from 1996 all HIV-infected IDU infected more than 6 years could have been found and treated immediately, 24% of HIV deaths could have been avoided, but prevalence would have been higher, and incidence would have dropped by only 6%. In this scenario, in total approximately three times as much cART was used compared to within the baseline scenario. When keeping the probability for finding a HIV-infected IDU at 0.01 each month, but treating independent of $CD4^+$ cell count, only one and a half times the baseline cART would have been used. This would have lowered incidence by 4%, but mortality by only 6%.

When treating from low $CD4^+$ cell count lowering of infectiousness by cART is largely offset by the lengthening of infectious life-time, hence prevention is clearly best served by early diagnosis and immediate treatment thereafter. We therefore, for various demographic settings, explored the effects of a test and treat strategy. We find that by such a strategy many new infections can be prevented; in a stable population of IDU, about half of all new infections within a 30-year period were avoided when IDU started treatment on average 1 year after becoming infected (corresponding to testing IDU on average once every 2 years) (Fig. 2a). HIV could even be eventually eliminated if IDU started treatment on average within 1.6 months after infection (corresponding to testing IDU once per 3.2 months, results not shown).

As HIV spreads quickly within the high-risk subpopulation, HIV incidence peaked very rapidly. Therefore, the test and treat practice had by far the largest impact when implemented soon after introduction of HIV into the population; initiating the test and treat strategy 2 years after the first HIV-cases are diagnosed prevented only

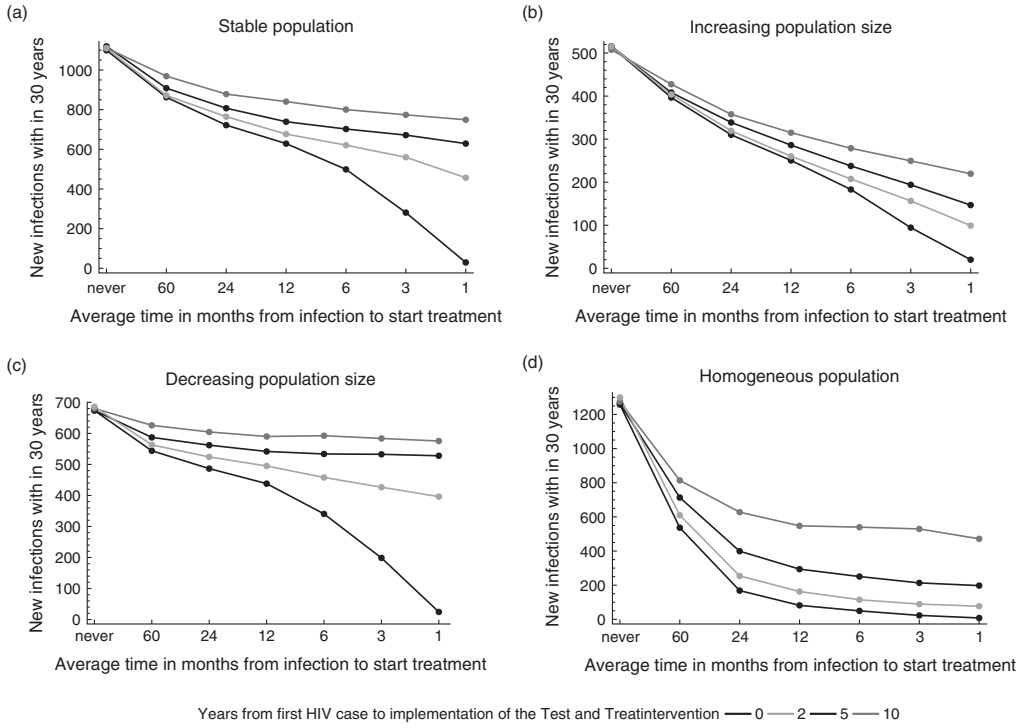

Fig. 2. Total incidence over a 30-year epidemic of HIV among injection drug users (IDU) as influenced by a test and treat strategy of combination antiretroviral therapy (cART). (a) Within a stable population of approximately 2000 IDU, each month four new IDU enter the population. (b) Within an increasing population of initially 200 IDU, each month four new IDU enter the population. (c) Within a decreasing population of initially 2000 IDU, no new IDU enter the population. (d) Within a stable population [as described for (a)], but all IDU borrow and lend out 2.5 syringes each month. For (a), (b) and (c), 31% of new IDU are high-risk, these share six, and remaining low-risk IDU share 0.6 syringes per month. Seventy percent of sharing preferentially occurs with same risk IDU. Dots represent the average of 50 model runs; lines are for ease of reference only.

about two-thirds, and after 5 years about half of the cumulative number of infections over the first 30 years of the epidemic, even when all IDU started treatment 1 month after becoming infected. When the population of IDU was increasing over time, later introduction of the test and treat intervention still prevented a larger part of new infections (Fig. 2b). Conversely, with the IDU population declining (as it was for Amsterdam) later intervention had even less impact (Fig. 2c).

These results depend strongly on the heterogeneity of risk within the population. The risk distribution assuming that 31% of IDU taking 10 times the risk of remaining IDU, and that 70% of contacts occur preferentially with IDU of similar risk-level, was based on fitting our model to ACS data of HIV and HCV prevalence and incidence [10]. Assuming a homogenous population with respect to risk-behavior, the scope for a timely test and treat intervention was much enhanced, since initial HIV spread was much slower in such a population (Fig. 2d).

In the stable heterogeneous population, without intervention 48% of all new cases were due to infection from acutely (< 2 month) infected IDU (68% of the new infections within the first 5 years, 28% of infections from 5 to 30 years after the start of the epidemic) (results not shown). In the homogenous and the increasing IDU population 41%, but in the decreasing IDU population an even larger fraction, 57% of infections, was due to acutely infected IDU. This explains the rapid uptake of cART needed to eliminate HIV.

In a risk heterogeneous population, to increase efficiency, intervention might be targeted by risk level (Fig. 3). Incidence was lowered almost as much when limiting testing for HIV to only the 31% high risk IDU, compared to testing all IDU. Note however that total cART used in this scenario is also nearly equal to that when testing all IDU, since high risk IDU are much more likely to be infected than low risk IDU.

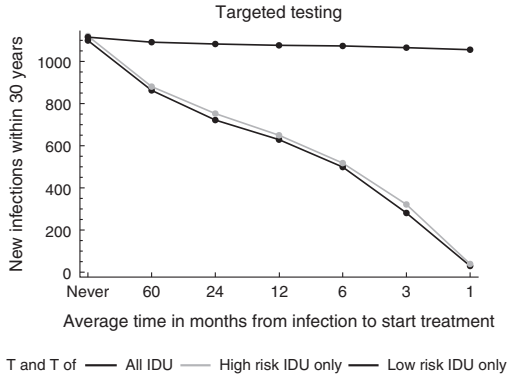

Fig. 3. Total incidence over a 30-year epidemic of HIV among injection drug users (IDU) as influenced by a test and treat strategy of cART, when targeting testing by risk behavior of the IDU. The intervention is implemented from the start of the epidemic. Dots represent the average of 50 model runs; lines are for ease of reference only.

Here we assume that HIV-diagnosis alone does not change risk-behavior. As an alternative intervention, HIV-infected tested IDU might receive counseling or they might be isolated in order to stop them from lending syringes to other IDU. Under most testing scenarios, we found such intervention to be much less effective than cART usage in lowering HIV incidence (Fig. 4). When one specific IDU stops lending out syringes, those that would have borrowed from this individual will borrow syringes from others instead. Many of the HIV-infected IDU are likely not yet diagnosed and treated, especially those acutely infected who are most infectious. Isolating HIV-infected IDU compared to test and treat would then replace borrowing from HIV-infected IDU using cART

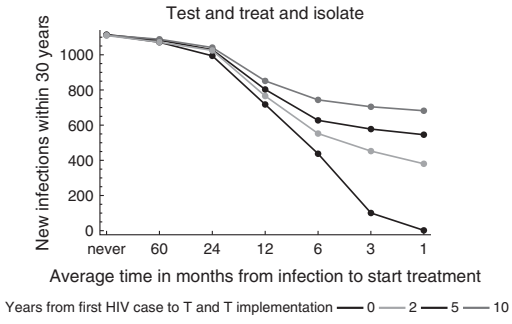

Fig. 4. Total incidence over a 30-year epidemic of HIV among injection drug users (IDU) as influenced by a test and treat strategy of combination antiretroviral therapy (cART), combined with intervention which isolates the identified HIV-infected IDU: these no longer share injecting equipment with others. Dots represent the average of 50 model runs; lines are for ease of reference only.

with borrowing from more infectious IDU, thereby increasing population incidence. Only at low HIV prevalence, for example in a scenario with very frequent and timely testing, isolating HIV-infected IDU could be more beneficial compared with cART use by the tested IDU.

Discussion

We adapted a model based on the Amsterdam IDU population in order to study the effects of cART on HIV incidence. From examining counter-factual scenarios, we concluded that use of cART only very slightly decreased incidence in Amsterdam. As IDU started treatment only at low $CD4^+$ cell counts, the effect of lowered infectiousness on transmission was mostly offset by increased survival, which increases the time they could infect others. Clearly for cART to lead to large population benefits, treatment should be started independently of $CD4^+$ cell count.

We therefore considered the possible benefits of a test and immediate treat strategy in a more generalized population of IDU. We found that such an intervention could prevent many new cases. For achieving a substantial reduction of incidence however, it is important that the test and treat strategy be implemented soon, within a few years of the first HIV cases entering an IDU population. Especially in IDU populations that are declining in size, most of the incidence will otherwise have already occurred at the moment of initiating the intervention.

There is ongoing debate as to whether the high infectiousness of individuals early after infection severely compromises the potential for treatment as prevention [22]. In our model, almost half of all new infections were caused by individuals within the acute stage, despite our relatively conservative choice of a 10-fold increased infectiousness [3]. This large proportion in our model is explained by the high HIV-transmissibility by injecting but a relatively short infectious-life-time of IDU (due to their relatively high death rate and cessation of injecting), and our focus on the early stage of the HIV epidemic. In our model elimination of HIV could occur, but only if the average time from infection to starting cART was within the 2-month period of acute infection.

Especially where harm reduction programs are already established that allow for regular contact with IDU, frequent testing for HIV infection may be achievable. However, only the actual implementation of a test and treat strategy will determine the successful uptake rate achievable within the IDU setting. For our model, we made the optimistic assumption that all IDU were willing to start treatment early, and that they would also be reasonably adherent, despite limited personal health benefits. In reality, this will pose a serious challenge [23–25].

With low adherence, viral load and thereby infectiousness remain higher [25], which could also boost the development of cART-resistant HIV-strains [26]. It would therefore be prudent to monitor adherence, preferably through viral load measurements [27]. Somewhat lower rates of cART adherence [28,29], correlated with lowered rates of viral suppression [30], have been reported for active IDU compared with ex-IDU or non-IDU, although a meta-analysis did not show increased risk of resistance to treatment within this group [31]. Adherence by IDU may be enhanced by for example peer counseling, mobile-phone alarms, or directly observed treatment [32].

Direct reliable information on risk behavior is rare. Here we based risk parameters on the model fit to HIV as well as HCV incidence and prevalence in Amsterdam [10], but we may have over- or underestimated the extent of the heterogeneity in this population, and different populations will have different risk distributions. In a more homogenous population initial spread of HIV will be slower, so that even at lower uptake rates later implementation of a test and treat strategy could still have great effects. A completely risk-homogenous population of IDU seems unlikely however, and this scenario should therefore be interpreted also as a warning against overly optimistic expectations that result from modeling studies that ignore population risk heterogeneity.

The test and treat strategy could be made more efficient if directed mostly at those with highest risk behavior. On the contrary, high risk IDU might be the ones most difficult to reach and least likely to adhere to treatment, in which case our analysis represents an overestimate of the benefits of cART provision. For a realistic cost–benefit analysis of different implementation strategies, information on uptake stratified by risk behavior would be required.

Where there is a low coverage of harm reduction programs, instead of or in addition to providing them with cART, HIV-infected IDU could be targeted for counseling, or they might even be isolated forcefully by imprisonment, to stop them from lending out their used syringes to other IDU. We found that even if HIV-infected IDU would stop lending out syringes completely it would have less impact than treating them with cART at all but very low HIV prevalence.

In conclusion, we have shown that provision of cART to all HIV-infected IDU could lead to great reductions in HIV incidence. Previous modeling studies on the use of TasP have pointed to the optimistic prospect for complete elimination of the sexual spread of HIV [5,33]. We conclude that among IDU however, only unrealistically high uptake rates from very early after infection would allow cART provision by itself to eliminate HIV. In accordance with previous modeling studies on IDU, we therefore recommend an integrated approach of several different harm reduction strategies [8,9,34].

In countries confronted with a sudden rise of injecting drug users, rapid implementation of harm reduction services combined with regular testing for HIV and prompt treatment may avoid the spread of HIV. Behavioral intervention should be directed at those not yet infected; by injecting with fewer used syringes, IDU lower their risk of infection of HIV, but also their risk of other blood-borne infections such as HCV. Possibly, efficiency of these interventions and treatment as prevention could be enhanced by targeting specific risk-behavior sub-groups within the IDU community [35].

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Conflicts of interest

There are no conflicts of interest.

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Appendix to: Treatment as prevention among injecting drug users; extrapolating from the Amsterdam cohort study, de Vos AS, Prins M, Coutinho RA, van der Helm JJ, Kretzschmar MEE. Created 9th of December 2013.

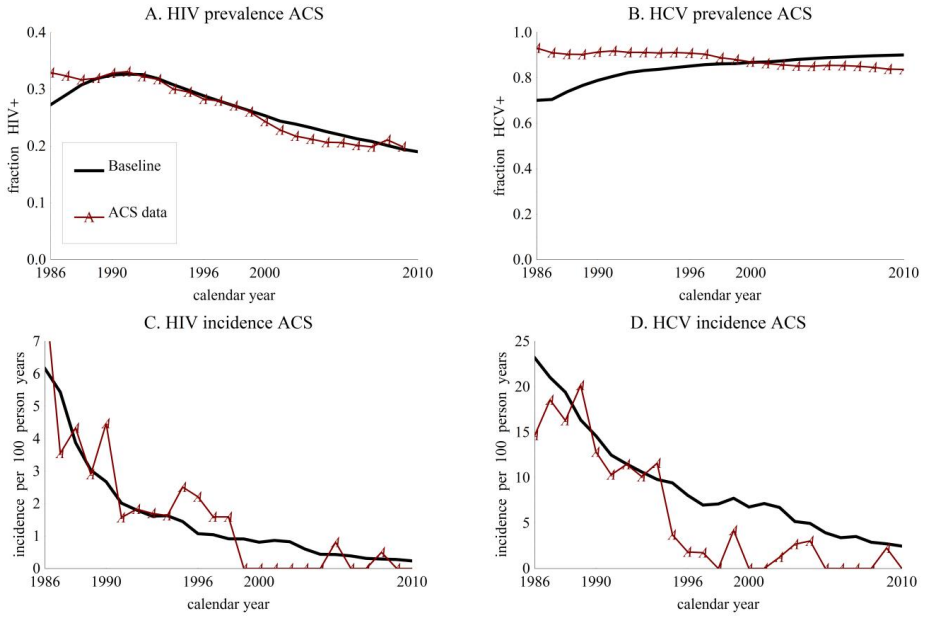

Figure A1. HIV and HCV incidence and prevalence within the modeled cohort as compared to data from the actual Amsterdam Cohort Studies (ACS) among IDU, for the baseline scenario. Since direct measurements for risk behavior were lacking, syringe sharing rate parameters were chosen based on this model fit to ACS incidence and prevalence data (see also reference 10).

AIDS was first reported in Amsterdam in 1982, with a first IDU AIDS case reported in 1985 [10]. The quick spread of this disease among Amsterdam IDU could only be reproduced in our model by assuming a high-risk subgroup of individuals sharing syringes mostly among themselves, while lower risk by remaining IDU limited the maximum HIV prevalence reached. High HCV prevalence among all IDU indicated the non-negligible risk level of these remaining IDU.

One cause for the lowered HIV and HCV incidence in the model over calendar time was a cohort-effect due to the limited inflow of new IDU from 1985 onwards; high-risk IDU were infected first, leaving mostly low-risk IDU at risk for infection. Also, the fraction of ACS participants actively injecting declined over time; a criterion for ACS recruitment was recent injecting, but IDU that stopped injecting remained as participants. HIV prevalence decreased as HIV-related mortality mainly affected the high-risk subgroup, decreasing the total level of population risk over time.

Our baseline model slightly underestimated the actual decline in HCV incidence from the mid-1990s, and showed a slight increase rather than a slight decrease in HCV prevalence over time. This may indicate that the actual Amsterdam IDU lowered their risk-behavior over calendar time, perhaps under influence of harm reduction interventions [10]. We do not assume such behavior change here, in order to keep the model interpretation as straight forward as possible.

CHAPTER 5

The efficiency of targeted intervention in limiting the spread of HIV and Hepatitis C Virus among injecting drug users

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The efficiency of targeted intervention in limiting the spread of HIV and Hepatitis C Virus among injecting drug users

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HIGHLIGHTS

- Intervention on IDU may be made more efficient by targeting specific risk subgroups.
- HIV might be substantially reduced or eliminated by targeting high risk IDU only.
- To lower HCV incidence most targeting lower risk IDU may be optimal.

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ABSTRACT

Background. Interventions aimed at minimizing the spread of blood borne infections among Injecting Drug Users (IDU) are impeded by limitations in resources. To enhance their efficiency, it may be beneficial to target specific behavioural subpopulations, distinguished by syringe sharing tendencies.

Methods. We used mathematical modelling to explore the effects of two types of intervention: removal of individuals from the injecting population and risk decrease at group-level (e.g. distribution of syringes). We computed the direct effects of intervention on the probability of obtaining and spreading infection as a function of baseline risk behaviour. Population level effects of (targeted) intervention were explored using a differential equations model, which incorporated two levels of risk.

Results. Within most scenarios of risk distribution considered, HIV could be substantially reduced or eliminated by targeting high risk IDU only. Conversely, higher incidence reductions for HCV were reached in many scenarios when targeting low risk IDU. The potential for preventing infections by removal of uninfected IDU increases with baseline risk, but so does the probability that an IDU is already infected before being reached by intervention. Decreasing risk is likely to only delay rather than prevent infection for IDU borrowing many syringes, especially for a very infectious disease such as HCV.

Conclusions. The efficiency of intervention on injecting drug users may be much enhanced by targeting specific risk subgroups. However, the optimal targeting policy depends strongly on the infection under consideration.

1. Introduction

Through the sharing of contaminated syringes blood borne infections are spread among injecting drug users (IDU). Almost one-third of all new HIV infections outside of sub-Saharan Africa are acquired via this infection route (Mathers et al., 2008). Commonly within IDU populations, from 50% to 90% of individuals are infected by the Hepatitis C Virus (HCV) (Hagan and Des Jarlais, 2000). Injecting drug use is in the beginning stages in certain regions of China, Russia and India (Grassly and Garnett, 2005). In parts of Europe injecting drug use has been declining (EMCDDA, 2012). However, over a third of heroin users here do still use this route of administration, so that also here it remains a major public health issue.

Efforts to lower incidence of infection among IDU include needle and syringe exchange programs, opiate substitution (methadone) treatment and risk education programs, collectively known as harm reduction policy. Evidence supporting usefulness of such programs is accumulating, particularly for HIV, despite the complicated nature of performing unbiased research on this issue (Palmateer et al., 2010; Turner et al., 2011; Hagan et al., 2011; Van Den Berg et al., 2007).

Especially as injecting drug use often occurs in more resource limited countries, interventions should be made as cost-effective as possible (Mathers et al., 2010). This point was exemplified

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recently by a serious HIV outbreak in Greece; budgets were cut on risk prevention among Greek IDU due to the financial crisis (Pharris et al., 2011).

Concentrating intervention effort on subgroups distinguished by their risk for contracting or spreading infection has the potential to enhance intervention efficiency. This has been shown for example by models on vaccine intervention (Anderson and Hanson, 2005; Chow et al., 2011; Koopman et al., 2005; Dodd et al., 2010). Injecting drug users constitute a high risk group for HCV and HIV infection within the general populations (Des Jarlais and Padian, 1997), but among injecting drug users there may still be great diversity in risk for infection; tendencies to reuse syringes are likely related to personal circumstances such as poverty and homelessness and/or to psychological factors (Nordén and Lidman, 2005; Hutchinson et al., 2000).

Vickerman and Hickman (2010) projected the impact of a generic intervention among IDU; in their simulation, syringe sharing frequency was reduced by 50% for all, for all high, or for all low frequency syringe sharers. They noted that intervention on all or all high risk IDU had generally much less impact on the HCV than on the HIV epidemic. Intervention on the low risk IDU had reduced impact on HIV, but contrarily, greater impact on HCV incidence.

Here we investigate the impact of two different types of intervention on transmission of disease among IDU. We consider how much incidence is lowered per prevented risk act (i.e. when providing clean syringes), or per individual risk behaviour change (i.e. when educating or isolating IDU). Using an analytic approach we derive explicit expressions, relating the number of infections prevented to population prevalence, disease characteristics, and risk level of the IDU under intervention. This allows for a mechanistic understanding of intervention effects, explaining the optimal targeting strategy as identified in a deterministically modelled population of IDU.

2. Methods

We considered two types of intervention, which we refer to as removal intervention and risk decrease intervention. These two interventions are distinguished by the moment of implementation during an individual's injecting career and the level of risk decrease (see Fig. 1). Removal intervention represents intense individual based intervention which would prevent all further risk acts of an IDU, for example by isolation within a clinic or sufficient substitution (methadone) treatment. For such intervention individuals first have to be reached, which is likely to occur only later within their injecting career.

Risk decrease intervention represents the distribution of syringes, cleaning products, or providing education. Such intervention generally occurs with a low threshold and on a group level; syringes and information may be obtained directly from programs or indirectly through other injectors. This intervention is therefore expected to reach IDU from the start of their injecting career, but to only lower rather than prevent all risk for a group of IDU.

We studied the impact of these interventions on two different levels. We first studied the direct effects of intervention on one single individual, by calculating the probability of preventing infection of this one IDU under intervention, as well as the expected number of infections amongst others prevented. We examined this preventive potential as a function of risk behaviour without intervention (the baseline risk). Secondly, we considered the impact of intervention on HCV and HIV incidence at the group level, which includes both direct and indirect (through prevalence changing) effects. For this we used a differential equations model which incorporated two levels of risk. We compared effects when implementing intervention on all IDU with effects when concentrating intervention effort on either of the two risk subgroups.

2.1. Individual level calculations

Preventing primary infection. The probability that intervention prevents infection for an index IDU (primary infection) is calculated by subtracting the probability that someone becomes infected despite intervention from the probability that someone would have become infected without intervention (see Fig. 1).

In our calculations r represents the baseline risk of the index in syringes borrowed per month. Intervention lowers this risk by r_r borrowing events per month. By p we denote the (infection specific) probability of infection through use of a syringe carrying infection. We assume that an endemic state for the population of IDU has been reached, in which the proportion of all syringes lend out that carry infection (the infection prevalence among syringes) is m. Individuals leave the population, by dying or other non-intervention related stopping of injecting, with rate μ.

Without intervention, a susceptible individual either becomes infected with force of infection rpm or stops injecting before this time with rate μ, so that the probability to ever become infected is $rpm/(\mu+rpm)$. To calculate the lifetime probability of infection in the presence of intervention, r is replaced by $r-r_r$.

Intervention can only prevent infection if the index IDU is uninfected when intervention starts, this probability we denote by u. The probability of preventing primary infection, κ_p, is then described by

$$\kappa_p = u\left(\frac{rpm}{\mu+rpm}-\frac{(r-r_r)pm}{\mu+(r-r_r)pm}\right)$$

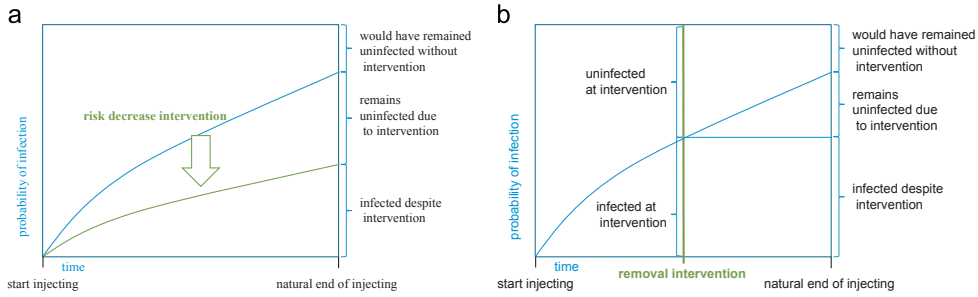

Fig. 1. The effect of two types of intervention on the life-time probability for an IDU to acquire infection. (a) By risk decrease intervention we lower risk in syringes borrowed per unit of time from the start of an IDU's injecting career. (b) By removal intervention we discontinue all risk from a random moment within an IDU's injecting career.

For risk decrease intervention we assume that the index is immediately reached, i.e. $u=1$. For removal intervention we assume that an IDU is reached at a random moment within their injecting career, and that all risk is prevented from this moment of intervention onwards. The probability of not being infected when intervention starts is in this case a weighted average over the probability to still be injecting at a time τ after start injecting and the probability of being uninfected at that time, i.e. for removal intervention we find

$$u=\frac{\int_0^\infty e^{-\mu\tau}e^{-rpm\tau}\,d\tau}{\int_0^\infty e^{-\mu\tau}\,d\tau}=\frac{\mu}{\mu+rpm}\quad\&\quad r_r=r\Rightarrow\kappa_p=\frac{\mu rpm}{(\mu+rpm)^2}$$

Preventing secondary infections. Intervention may also prevent the individual under intervention from spreading infection to others. We assume a strict tit for tat syringe exchange situation, that is the number of syringes lend out by an individual will equal the number of syringes borrowed per month r. We first calculate the expected number of infections caused by an individual without intervention, and subtract the number of infections caused despite intervention.

Over the complete remaining injecting career of an individual, without intervention, we expect a number of syringes lend out whilst infectious equal to

$$(1-u)\int_{\tau=0}^{\tau=\infty}re^{-\mu\tau}\,d\tau+u\int_{\tau=0}^{\tau=\infty}re^{-\mu\tau}(1-e^{-rpm\tau})\,d\tau$$
$$=(1-u)\frac{r}{\mu}+u\frac{rpm}{\mu+rpm}$$

That is, for an IDU already infected all syringes lend out will be contaminated, for an IDU not yet infected we additionally multiply by the probability to have become infected at time τ. The number of syringes carrying infection lend out with intervention can be calculated by substituting r by $r-r_r$ within the integrals.

The probability that use of such a contaminated syringe leads to infection was defined as p. However, infection can only occur if the contaminated syringe is borrowed by an individual not yet infected. Due to our assumption that IDU lend out and borrow syringes at equal rates, the probability that a syringe is borrowed by an uninfected IDU equals $1-m$.

By intervention we prevent an expected r_r/μ syringes being lend out by a certain IDU, but the number of syringe exchanges is not altered for remaining IDU; borrowings from the individual under intervention will be replaced by borrowings from random other IDU. To properly calculate the effects of intervention, we have to take into account that these replacement borrowings may also lead to infection. A randomly borrowed syringe carries infection with probability m, in which case it causes infection (with probability p) only if it is borrowed by an uninfected IDU (with probability $1-m$).

Putting the above together, κ_s, the expected number of secondary infections prevented by intervention on one specific IDU, can be described by

$$\kappa_s=p(1-m)\left((1-u)\frac{r}{\mu}+u\frac{rpm}{\mu+rpm}\right)$$
$$-p(1-m)\left((1-u)\frac{(r-r_r)}{\mu}+u\frac{(r-r_r)pm}{\mu+(r-r_r)pm}\right)-p(1-m)\frac{r_r}{\mu}m$$

this simplifies to

$$\kappa_s=p(1-m)\left(\frac{r_r}{\mu}(1-m)-u\left(\frac{r}{\mu+rpm}-\frac{(r-r_r)}{\mu+(r-r_r)pm}\right)\right)$$

2.2. A population model

Spread of HCV and HIV. The model presented here is an adaptation of that discussed in de Vos et al. (2012). We consider a population divided into two subgroups of IDU, distinguished by their frequency of sharing, $\mathfrak{r}_l$ and $\mathfrak{r}_h$ for low risk and high risk IDU respectively. The parameter q represents the fraction of syringe sharing which takes place within risk subgroups, with the remaining fraction $1-q$ of sharing assumed to follow proportionate mixing.

For both HCV and HIV we distinguish between susceptible (S), acutely infected (I) and chronically infected (C) individuals, so that we have nine compartments per risk subgroup.

By p^C we denote the per HCV infected syringe use probability of becoming infected with HCV. For HIV acutely infected individuals are more infectious, we distinguish p^{H_A} and p^{H_C}. Individuals move out of the acute HCV phase with rate θ^C, where d gives the proportion of these infections being cleared and $1-d$ the proportion of infections leading to chronic HCV. Individuals co-infected with HIV have a modified probability d^H of clearing HCV. The rate of leaving the acute HIV phase is given by θ^H.

We assume constant recruitment rates B_l and B_h of susceptible IDU into the low and high-risk subgroups respectively, and constant rates of leaving the population μ_l and μ_h. μ^C is the additional death rate for chronically HCV-infected IDU, and μ^H the added death rate caused by HIV.

We introduce the notation $N_j=S_j^S+S_j^I+S_j^C+I_j^S+I_j^I+I_j^C+C_j^S+C_j^I+C_j^C$ where j represents the risk subgroup, h or l respectively. Main script denotes HCV status, superscript HIV status. $N_h+N_l=N$. Furthermore

$$f_j=\frac{N_j}{N},\quad \pi_j=\frac{I_j^S+I_j^I+I_j^C+C_j^S+C_j^I+C_j^C}{N_j},\quad\text{and}\quad \pi=f_l\pi_l+f_h\pi_h$$

where f_j is the fraction of individuals within subgroup j, π_j the endemic prevalence of HCV in subgroup j, and π the endemic prevalence of HCV in the overall IDU population. Assuming that individuals' rates of lending out syringes equal their borrowing rates we define the probability m^C that a randomly borrowed syringe carries HCV infection as

$$m^C:=\frac{\mathfrak{r}_lf_l\pi_l+\mathfrak{r}_hf_h\pi_h}{\mathfrak{r}_lf_l+\mathfrak{r}_hf_h}$$

The force of HCV infection λ_j^C can now be defined as

$$\lambda_j^C=\mathfrak{r}_jp^C(q\pi_j+(1-q)m^C)$$

Analogously, we denote the endemic prevalence of acute HIV by $\pi_j^{H_A}=(S_j^I+I_j^I+C_j^I)/N_j$ and the endemic prevalence of chronic HIV by $\pi_j^{H_C}=(S_j^C+I_j^C+C_j^C)/N_j$. Then the probability that a randomly borrowed syringe carries HIV from acute infection is $m^{H_A}=(\mathfrak{r}_lf_l\pi_l^{H_A}+\mathfrak{r}_hf_h\pi_h^{H_A})/(\mathfrak{r}_lf_l+\mathfrak{r}_hf_h)$ and that it carries HIV from chronic infection is $m^{H_C}=(\mathfrak{r}_lf_l\pi_l^{H_C}+\mathfrak{r}_hf_h\pi_h^{H_C})/(\mathfrak{r}_lf_l+\mathfrak{r}_hf_h)$. The force of infection for HIV is then given by

$$\lambda_j^H=\mathfrak{r}_jp^{H_A}(q\pi_j^{H_A}+(1-q)m^{H_A})+\mathfrak{r}_jp^{H_C}(q\pi_j^{H_C}+(1-q)m^{H_C})$$

The model is now defined by the system of equations

$$\frac{dS_j^S}{dt}=B_j+d\theta^CI_j^S-S_j^S(\mu_j+\lambda_j^C+\lambda_j^H)$$
$$\frac{dS_j^I}{dt}=\lambda_j^HS_j^S+d\theta^CI_j^I-S_j^I(\mu_j+\lambda_j^C+\theta^H)$$
$$\frac{dS_j^C}{dt}=\theta^HS_j^I+d^H\theta^CI_j^C-S_j^C(\mu_j+\mu^H+\lambda_j^C)$$
$$\frac{dI_j^S}{dt}=\lambda_j^CS_j^S-I_j^S(\mu_j+\lambda_j^H+\theta^C)$$

$$\frac{dI_j^I}{dt} = \lambda_j^C S_j^I + \lambda_j^H I_j^S - I_j^I(\mu_j + \theta^C + \theta^H)$$

$$\frac{dI_j^C}{dt} = \lambda_j^C S_j^C + \theta^H I_j^I - I_j^C(\mu_j + \mu^H + \theta^C)$$

$$\frac{dC_j^S}{dt} = (1-d)\theta^C I_j^S - C_j^S(\mu_j + \mu^C + \lambda_j^H)$$

$$\frac{dC_j^I}{dt} = (1-d)\theta^C I_j^I + \lambda_j^H C_j^S - C_j^I(\mu_j + \mu^C + \theta^H)$$

$$\frac{dC_j^C}{dt} = (1-d^H)\theta^C I_j^C + \theta^H C_j^I - C_j^C(\mu_j + \mu^C + \mu^H)$$

Intervention in a population with HIV and HCV. For the first type of intervention, removal intervention, we assumed that individual IDU can be prevented from borrowing and lending out syringes completely. In effect we remove IDU from the population. We assumed background mortality combined with a natural (non-intervention) rate at which individuals stop injecting μ, which is equal for the two groups. The intervention effort E_μ is the number of IDU removed per month by intervention. We implemented intervention on all IDU: $\mu_l = \mu_h = \mu + E_\mu/N$; on low risk IDU only: $\mu_l = \mu + E_\mu/N_l$ and $\mu_h = \mu$; or on high risk IDU only: $\mu_l = \mu$ and $\mu_h = \mu + E_\mu/N_h$.

For risk decrease intervention the total intervention effort is the number of syringe exchanges prevented per month, E_r. Without intervention low risk and high risk IDU respectively both borrowed and lent out r_l and r_h syringes per month. When intervention was not targeted, we assumed that each syringe exchange act had the same probability of being prevented, i.e. $r_l = r_l - (E_r/N_l)(r_l f_l/(r_l f_l + r_h f_h))$ and $r_h = r_h - (E_r/N_h)(r_h f_h/(r_l f_l + r_h f_h))$. When targeted to low risk IDU only: $r_l = r_l - E_r/N_l$ and $r_h = r_h$; when targeted to high risk IDU: $r_l = r_l$ and $r_h = r_h - E_r/N_h$.

We considered equilibrium states for the population, i.e. intervention has been implemented structurally for a considerable time so that HIV and HCV are at endemic steady state.

Parametrization and sensitivity to model assumptions. Parameter values of the differential equation model were chosen as in de Vos et al. (2012), where infection specific parameters were extracted from literature. These values are given in Table 1 of the Appendix. We first considered a population with risk behaviour based on questionnaire data from the Amsterdam Cohort Studies among IDU, specifically self-reported time since last borrowing a used syringe (de Vos et al., 2012). As we lack information on mixing between the different risk levels, we chose proportionate mixing ($q=0$) for this baseline scenario. However, segregation between the subgroups might be substantial (de Vos et al., 2013), therefore we also considered a much higher value for q (see Appendix 1). Additionally we studied sensitivity of the results to different risk levels (main text) and risk subgroup sizes (see Appendix 1).

We also considered how certain of our structural model assumptions determine our population level results. We used a simplified population model, which dispenses with disease specific factors (such as an acute phase for HIV and clearing for HCV), in order to more specifically asses the influence of the disease infectiousness p (see Appendix 2). We also considered less than complete removal intervention, that is, rather than preventing all further risk, preventing a fraction of future syringe sharing (see Appendix 3). Finally, we considered how strongly our results depend on the assumption of stable risk types, by allowing individuals to switch between risk levels (see Appendix 4).

3. Results

3.1. Individual level impact of intervention

We first examine the direct effects of intervention implemented on one single IDU.

Preventing primary infection. Recall that we described with κ_p the probability of preventing infection for one IDU under intervention. From this expression we see that for IDU uninfected at intervention ($u=1$), preventing an absolute number of syringe borrowings has highest probability of preventing infection for individuals with lowest baseline risk r (see Fig. 2a). The reason for this is that the life-time probability of infection saturates with risk (see Fig. 1). For higher risk IDU, preventing one syringe from being borrowed is likely to merely delay rather than prevent infection. We also conclude that decreasing risk of one individual by r_r syringes (with $r_r < r$) has more impact than decreasing risk of n individuals (each with risk r) by r_r/n syringes, i.e. a limited supply of syringes has most impact when distributed among fewer as well as lower risk IDU.

Contrarily, when we consider a type of intervention that prevents all of an individual's risk, $r_r = r$, most risk is prevented with greatest potential for preventing infection when targeting highest risk uninfected IDU. However, for intervention that does not reach individuals from the start of their injecting career, higher individual risk r will also increase the probability that the individual is already infected at the moment intervention starts. Therefore, if we intervene by removing an IDU from the population at a random moment within their career, we find a peaked curve of the probability of preventing primary infection over baseline risk r (see Fig. 2b). For a more infectious virus, higher p, intervention will more often be too late, so that this peak lies more towards lower risk.

Preventing secondary infections. The first thing we note about expression κ_s, which gives the expected number of secondary infections prevented, is that it can become negative; intervention can increase the number of infections among those not under intervention (Fig. 2c and d). This occurs only for intervention on individuals with very low risk. These 'protect' the population since syringes borrowed from them are less likely to carry infection than syringes borrowed from random other IDU. With greater risk r, syringes lend out are more likely to carry infection, and the number of expected secondary infections prevented by intervention increases. However, the number of infections prevented saturates to $(r_r/\mu)(1-m)p(1-m)$ over r when intervention prevents an absolute number of borrowings only.

We find that the expected number of secondary infections prevented when intervening on a higher risk IDU often remains small compared to the probability of preventing a primary infection when intervening on a lower risk IDU. This is in great part due to the assumption of replacement borrowing, which makes prevention of secondary infections less likely.

The number of expected secondary infections caused by one individual increases with transmission probability p, giving greater potential of preventing secondary infections by intervention. However, for a more infectious virus, endemic equilibrium prevalence and thereby m is also higher. This renders prevention of secondary infections very difficult if there is replacement borrowing. When not borrowing from the infected index, borrowing is from a random other IDU, who is very likely also infected. Therefore at high viral infectiousness prevention of secondary cases generally becomes much less effective compared to primary infection prevention (see also Appendix Figure 3).

Additional disease induced mortality decreases the potential for individuals to spread infection, i.e. if mortality is taken into account the estimate of secondary infections prevented is lower. Also m decreases so that intervention is on time more often. In fact intervention effects for a virus that induces high mortality are comparable to those of a less infectious virus (results not shown).

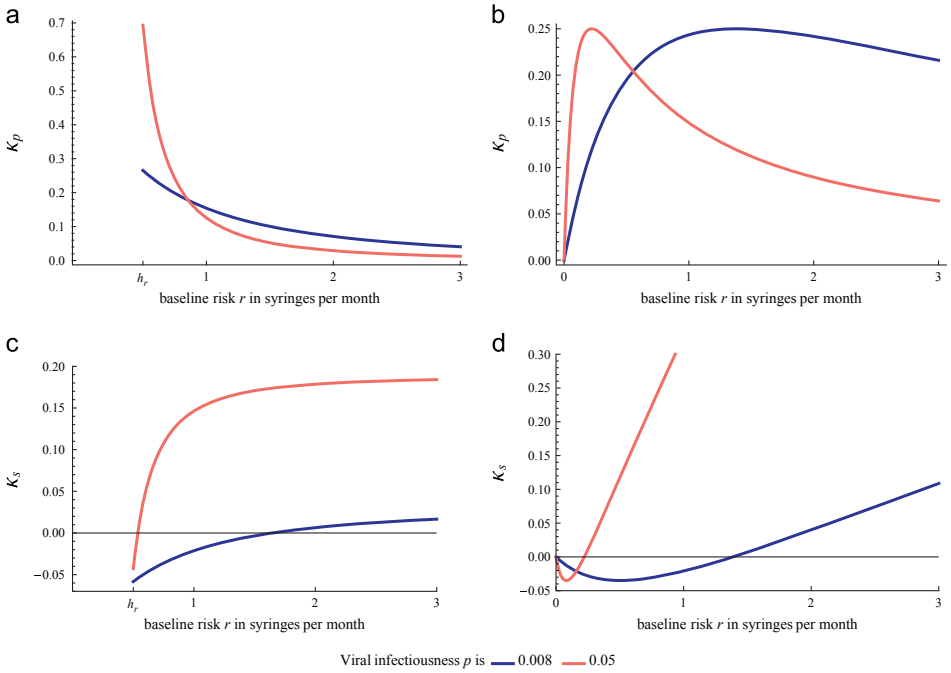

Fig. 2. Probability of preventing a primary infection and the expected number of secondary infections prevented by intervention on a single individual (equations κ_p and κ_s respectively), shown for two levels of viral infectiousness p ($p=0.008$ accords with infectiousness of chronic HIV, $p=0.05$ with the much higher infectiousness of HCV, see Appendix Table 1). $\mu=0.0083$ per month, $m=0.75$. Risk decrease intervention is immediate, so that IDU are uninfected at intervention, $u=1$, and risk is here lowered by $r_r=0.5$ syringes per month. For removal intervention $u=\mu/(\mu+rpm)$, i.e. an individual is removed at a random moment within their drug using career, and $r_r=r$, all risk is prevented from intervention onwards. (a) Preventing primary infection by risk decrease intervention, (b) Preventing primary infection by removal intervention, (c) Preventing secondary infections by risk decrease intervention and (d) Preventing secondary infections by removal intervention.

3.2. Population level impact of intervention

When implemented structurally, intervention has additional indirect effects, in that it changes disease prevalence and population structure. We first consider a population with risk based on data from the Amsterdam Cohort Studies among IDU (de Vos et al., 2012); 58% are low risk IDU, and unless reached by intervention these share $r_l=0.65$ syringes per month, while the 42% high risk IDU share $r_h=4.76$ syringes per month.

Risk decrease intervention. For lowering HCV incidence it is most efficient to lower the risk of IDU within the low risk subgroup (see Fig. 3a). This is as expected from the above analysis on individual level: intervention on low risk IDU prevents more primary infections per prevented borrowing act. Although intervening on high risk IDU will prevent somewhat more secondary infections, very few secondary infections can be prevented by any targeting strategy, due to replacement borrowing and high HCV prevalence. When all borrowing within the low risk subpopulation is prevented, further benefits can only be gained by distributing syringes within the high risk subgroup.

On the population level there is a threshold in risk below which an infection cannot persist. This is when the number of secondary infections caused by one infected individual in a completely susceptible population, R_0, is smaller than one (Diekmann et al., 2010). In the modelled population there is a qualitative difference between HIV and HCV, in that in a population of low risk IDU $R_0>1$ only for HCV but not for HIV. As a result HIV can be eliminated by decreasing risk for the high risk IDU only (see Fig. 3c). Relatively little can be gained in terms of HIV incidence prevented by distributing syringes within the low risk subgroup, as low risk IDU are much less likely to ever become infected by HIV.

Removal intervention. In terms of HCV infections prevented per IDU removal, at lower intervention effort it is most efficient to remove low risk IDU (see Fig. 3b). However, at higher intervention effort targeting high risk IDU becomes more efficient. As explained above, for a very infectious virus like HCV, preventing primary infection is more likely by removing low risk IDU (high risk IDU are likely already infected before being reached by intervention). However, with greater removal rate, the individual time since first injecting decreases within the population. Also the overall prevalence of infection and thereby the force of infection rpm is lowered. Therefore at high enough intervention effort removal will be on time for most high risk IDU.

Since HIV is less infectious, targeting high risk IDU is most efficient for lowering incidence of this infection at any level of intervention effort (see Fig. 3d). In fact, since HIV is almost exclusively spread among high risk IDU, targeting high risk IDU only can potentially remove HIV from the population completely. To remove HCV completely on the other hand, very effective intervention on both groups is necessary. In fact, nearly the entire IDU population would have to be removed in order to achieve this.

3.3. Effects of risk distribution on intervention

The potential for (targeted) intervention to lower incidence of infection depends on the distribution of risk within a population.

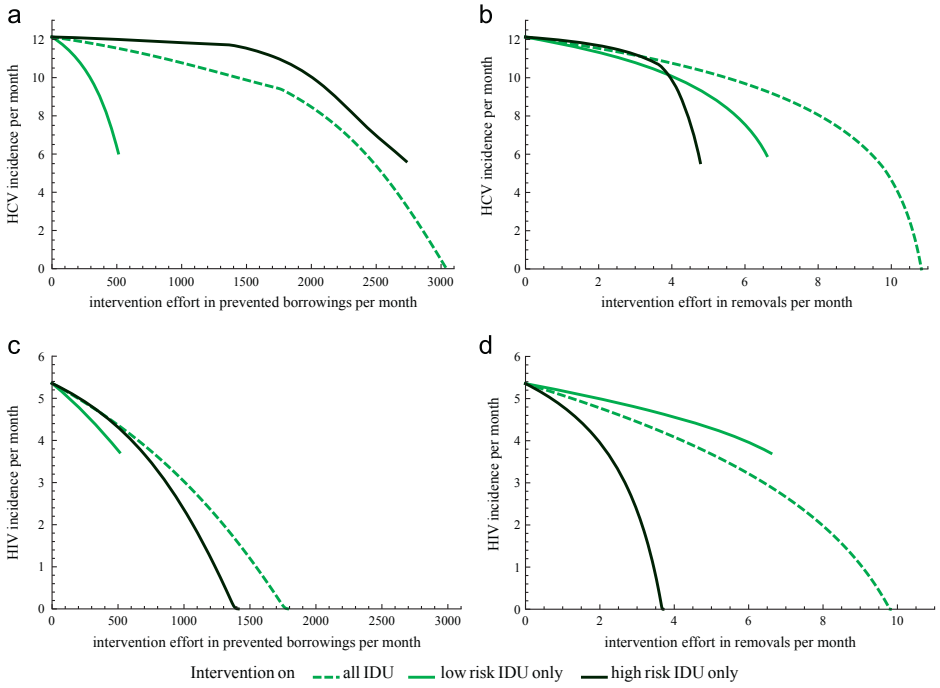

Fig. 3. Effects of intervention on the incidence of HIV and HCV for two types of (targeted) intervention. By risk decrease intervention random borrowing acts are prevented. By removal intervention random IDU are taken from the IDU population. Intervention is untargeted or targeted only at high or only at low risk IDU. Lines end when all risk is prevented in the targeted subgroup (figures a and c) or when all IDU are removed from the targeted subgroup (figures b and d). 58% of newly recruited IDU are low risk, without intervention these borrow and lend out 0.65 syringes per month, remaining IDU borrow and lend out 4.76 syringes per month. We assume proportionate mixing. Without intervention population size N is 1000. Remaining model parameters are as given in Table A1. (a) Risk decrease intervention effects on HCV incidence, (b) Removal intervention effects on HCV incidence, (c) Risk decrease intervention effects on HIV incidence and (d) Removal intervention effects on HIV incidence.

The optimal intervention strategy by risk heterogeneity. In Fig. 4 we show when targeting low risk or rather high risk IDU is most efficient in preventing infections for a range of risk and risk heterogeneity values. Risk heterogeneity is here defined as the ratio of risk taken by high risk individuals divided by that of low risk individuals.

At low intervention effort, both for HCV and HIV, risk decrease intervention is usually most efficient on low risk IDU (see Fig. 4a and c). As explained above, one syringe sharing act prevented has greatest potential of preventing primary infection for low risk IDU. At very low population risk, targeting high risk IDU is more efficient, as this prevents more secondary infections. As also discussed above however, even at maximal effort targeting low risk IDU may decrease incidence only minimally, especially for HIV. For a large range of population risk values, HIV may be eliminated with sufficient effort targeted at only high risk IDU.

As HCV is highly infectious and removal of high risk IDU therefore usually too late, we find a large range of population average risk for which removal of low risk IDU is most efficient in lowering incidence of HCV (see Fig. 4b). Contrarily for HIV, removal of high risk IDU is most efficient unless average population risk is very high, in which case also many low risk individuals would become infected with HIV without intervention (see Fig. 4d).

Relative size of the risk subgroups. By the individual based calculations we found that risk decrease intervention is most efficient when distributing syringes among fewer IDU. For removal intervention, average time to intervention is decreased by greater concentration of intervention effort, so that removal of individuals is more often on time (before infection has already occurred). For both types of intervention therefore, especially at higher levels of intervention effort, the smaller a risk group is the more favourable it is to target it (see Appendix Figure 1).

Less mixing between groups. When syringe sharing occurs less often between IDU of different risk types (higher q), little is changed in terms of the optimal targeting strategy for HCV, but for HIV it becomes most efficient to intervene on high risk IDU for a larger range of risk parameters (see Appendix Figure 2). When $R_0 < 1$ in a population of only low risk IDU, most infections of low risk IDU are caused by sharing with high risk IDU. With less interaction between subgroups, even fewer low risk IDU contract infection, and intervention on this subgroup has even less potential for preventing infections. As HCV is more infectious, HCV prevalence is usually high within both risk groups, so that who one shares with is of less consequence for effects of intervention on this disease.

3.4. Impact of model assumptions

Without disease specific complexities and interactions between HIV and HCV, modelled intervention effects are remarkably similar to those found using the full population model (see Appendix Figures 4 and 5). This shows that infectiousness of a disease, p, will to a great extent determine which targeting strategy is optimal for preventing transmission.

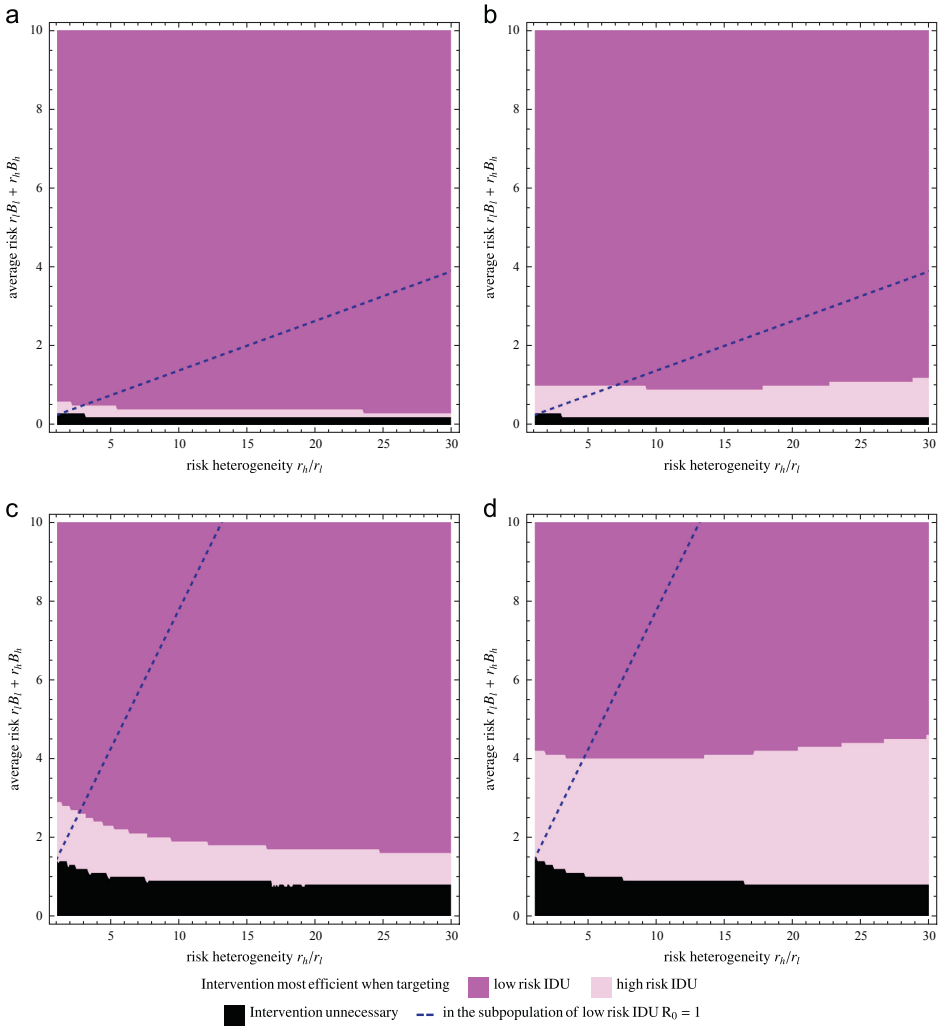

Fig. 4. The most efficient intervention strategy (targeting low risk IDU or targeting high risk IDU) for different distributions of risk within the population, at little intervention effort (i.e. rate of removal intervention is 0.00001 IDU per month, risk decrease intervention is 0.0001 syringes per month). We assume two risk groups of equal size. At low average risk infection does not spread, intervention is redundant. Below dashed lines intervention on high risk IDU only, at high enough intervention effort, has the potential of eradicating infection from the population. That is, risk of low risk IDU is too low to sustain spread of infection in a population of only low risk IDU ($R_0 < 1$). Remaining model parameters are as given in A1. (a) Optimal risk decrease strategy for HCV, (b) Optimal removal strategy for HCV, (c) Optimal risk decrease strategy for HIV and (d) Optimal removal strategy for HIV.

For less than complete removal, the effects of intervention are, unsurprisingly, smaller (see Appendix Figures 6 and 7). Importantly however, results are not affected qualitatively, specifically, which risk group to optimally target does not change when changing the fraction of risk reduction. With 75% rather than 100% decrease in risk, HCV incidence reduction already becomes minimal, while for HIV, substantial incidence reduction may still be expected from intervention that lowers high risk by 50%.

In order for intervention efficiency to be enhanced by targeting specific risk types, individual risk behaviour should be relatively stable (see Appendix Figures 9 and 10). We find that when all IDU are prone to switching between low and high risk behaviour at an average of more than about once per 20 months, targeted and untargeted intervention have very similar effects. We note however that switching does not influence who should be best targeted.

4. Discussion

The efficiency of intervention, in terms of infections prevented per prevented borrowing act or per IDU removal, may be much enhanced when intervention effort is concentrated on certain behavioural subgroups. However, whether efficiency is greatest when targeting low risk or high risk taking individuals depends strongly on the infection under consideration. Within most scenarios of risk distribution that we considered, HIV could be

substantially reduced or eliminated by targeting high risk IDU only. Conversely, for HCV higher incidence reductions were often reached when implementing a strategy of targeting low risk IDU.

Earlier modelling work has considered the effectiveness of targeted intervention (Anderson and Hanson, 2005; Chow et al., 2011; Koopman et al., 2005; Dodd et al., 2010). These studies examined interventions that lower susceptibility or infectiousness of individuals by for example a cure or vaccine. For such interventions it is generally best to target those individuals that both contract and spread infection most. In contrast, as was first shown by Vickerman et al., in certain settings risk prevention among IDU might be best targeted towards lower risk taking individuals (Vickerman et al., 2007; Vickerman and Hickman, 2010). In our study we have shown this to be a general result for different types of intervention and under a large range of population risk distribution. We have also clarified the individual level mechanisms behind this finding, noting in particular the importance of replacement borrowing.

Replacement borrowing means that when we prevent one IDU from sharing syringes, remaining IDU will borrow from other IDU instead. This makes prevention of secondary infections much less likely, especially for a highly prevalent infection like HCV. Intervention efficiency is then mostly determined by the potential for preventing primary infection. Due to the high infectiousness and high endemic prevalence of HCV, removal of higher risk IDU is often too late to prevent their infection with HCV. Also, preventing one borrowing act by a high risk individual is likely to merely delay rather than prevent their infection. For this last reason also, a large reduction of risk by few IDU will generally have greater impact than a small risk decrease by many IDU.

The potential for targeted intervention naturally depends on the actual existence and identification of different risk types. Self-reported risk generally shows great heterogeneity (Nordén and Lidman, 2005; Hutchinson et al., 2000; Garfein et al., 1996; Sutton et al., 2008), but less is known about how stable such risk behaviour is (Sutton et al., 2008; Genberg et al., 2011). There could be specific venues (shooting galleries) or geographic locations where sharing is frequent, and higher risk IDU might be reached more often in homeless shelters or prisons (Philbin et al., 2008).

Conversely, risk behaviour might be associated with the willingness of individuals to enrol in intervention programs. Our model can also be interpreted inversely, as showing the impact such differential intervention uptake would have on expected intervention effects. For example, if highest risk IDU are least willing to participate in intervention programs, decrease in HIV incidence by these programs would be more limited.

Although we only showed the expected benefits of structurally implementing intervention on the long term, that is for equilibrium HIV and HCV prevalence, the individual based probability calculations give an indication of what can be expected as more short term effects of (targeted) intervention. The understanding gained from these calculations may also be applied to other diseases, and might be useful in designing alternative intervention strategies.

Intervention effectiveness might be enhanced by testing for infection status. For example those not yet HCV infected could be targeted. Additional benefits could accrue if IDU change their behaviour by knowing their HIV status (Li et al., 2012; Norden et al., 2009). However, obligatory testing would greatly compromise the low threshold setting of syringe exchanges, and questions of ethics and additional costs would have to be considered. Alternatively, as a proxy for the probability of already being infected, intervention could be targeted by time since onset of injecting or age (Anderson and Hanson, 2005; Corson et al., 2012), a concept which might still be explored further for IDU. Targeting by risk type may also be worth investigating for other interventions, such as HCV treatment.

In conclusion, where resources are limited, targeted intervention should be considered for lowering incidence of HCV and HIV among IDU. Although this requires information about the actual risk taken by local (subgroups of) IDU, intervention benefits could be greatly enhanced. When elimination of HIV is the main focus, especially high risk individuals should be targeted, for example for isolation in clinics. To lower HCV incidence most effectively a limited number of syringes could be distributed among a smaller group of lower risk individuals only. To eliminate HCV however, intervention would eventually need to reach all IDU (Mathers et al., 2010).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jtbi.2013.05.017.

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Appendix to: The efficiency of targeted intervention in limiting the spread of HIV and Hepatitis C Virus among injecting drug users

De Vos AS, Kretzschmar MEE, April 2014

Contents

Table A1: Parameters and their values as used for the numerical results

Parameter	Value	Description
θ^C	0.33 per month	Loss rate of HCV acute status
θ^H	0.50 per month	Loss rate of HIV acute status
d	0.26	Probability of clearing HCV for HIV free IDU
d^H	0.15	Probability of clearing HCV for HIV-infected IDU
p^{H_C}	0.008 per syringe	Infectiousness chronic HIV
p^{H_A}	0.08 per syringe	Infectiousness acute HIV
p^C	0.05 per syringe	Infectiousness HCV
μ	0.0083 per month	Death and stop injecting rate for uninfected IDU
μ^+	0.002 per month	Additional death rate due to HCV infection
μ^H	0.0049 per month	Additional death rate due to HIV infection

For explanation of these chosen parameter values see de Vos et al 2012 [19].

1 Group size and mixing effects

Here we study the influence that relative group size and the level of mixing between the two risk-subgroups has on the optimal intervention strategy.

Methods

We vary relative size of the subgroups by varying the fraction of new IDU that take low risk, $\frac{B_l}{B_l+B_h}$. We study the influence of the level of mixing between the risk subgroups by varying q. $1-q$ is the fraction of syringe sharing which takes place preferentially within subgroups, so that for $q = 0$ (as in our baseline scenario) IDU mix completely at random, and for $q = 0.9$ (the situation considered here) almost all syringes are shared among IDU with similar risk.

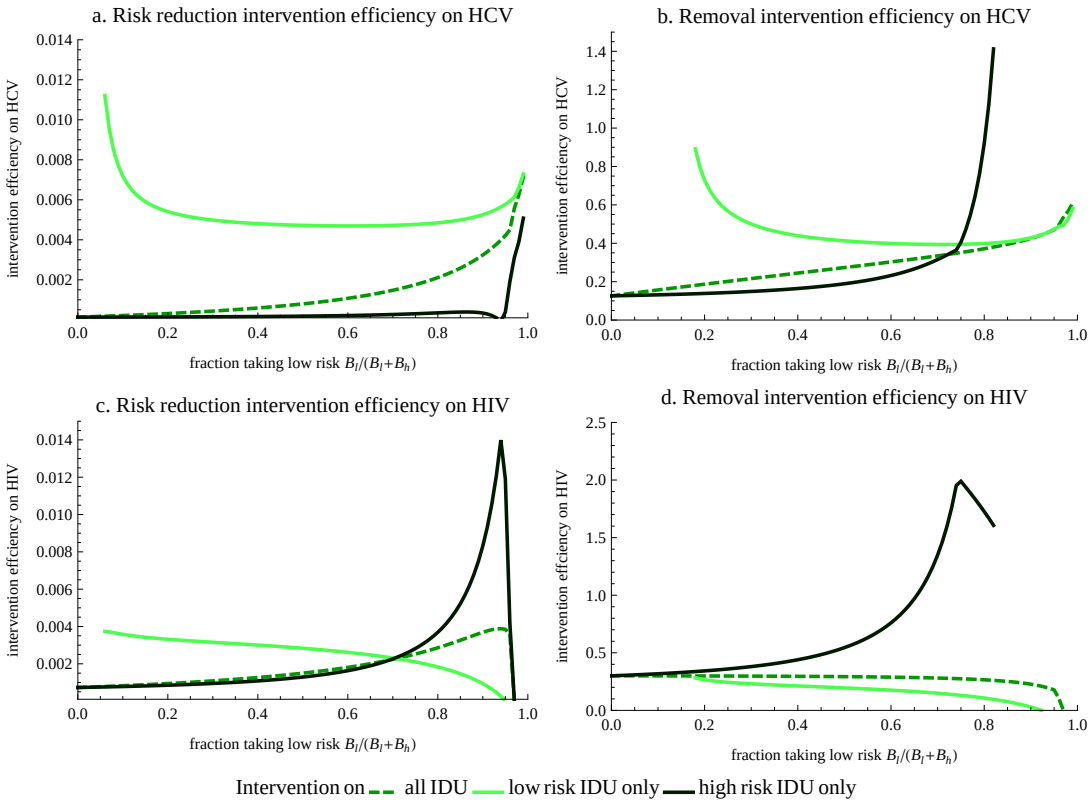
Results

Intervention is generally more efficient when it is concentrated within a smaller subgroup (see figure A1). As explained in the main text, it is better to much decrease risk of a few IDU than to slightly decrease risk for many IDU (since the probability

to become infected saturates with risk). A limited supply of syringes therefore has most impact when distributed within a smaller subgroup (figures A1a and A1c). For removal intervention, concentrating effort within a smaller subgroup lowers the average time to intervention (figures A1b and A1d). However, relative group size also has an effect on intervention efficiency through viral prevalence. For example, when almost all IDU take low rather than high risk the probability of borrowing an infected syringe (m) much decreases, which increases the intervention efficiency on low risk IDU (figures A1a and A1b).

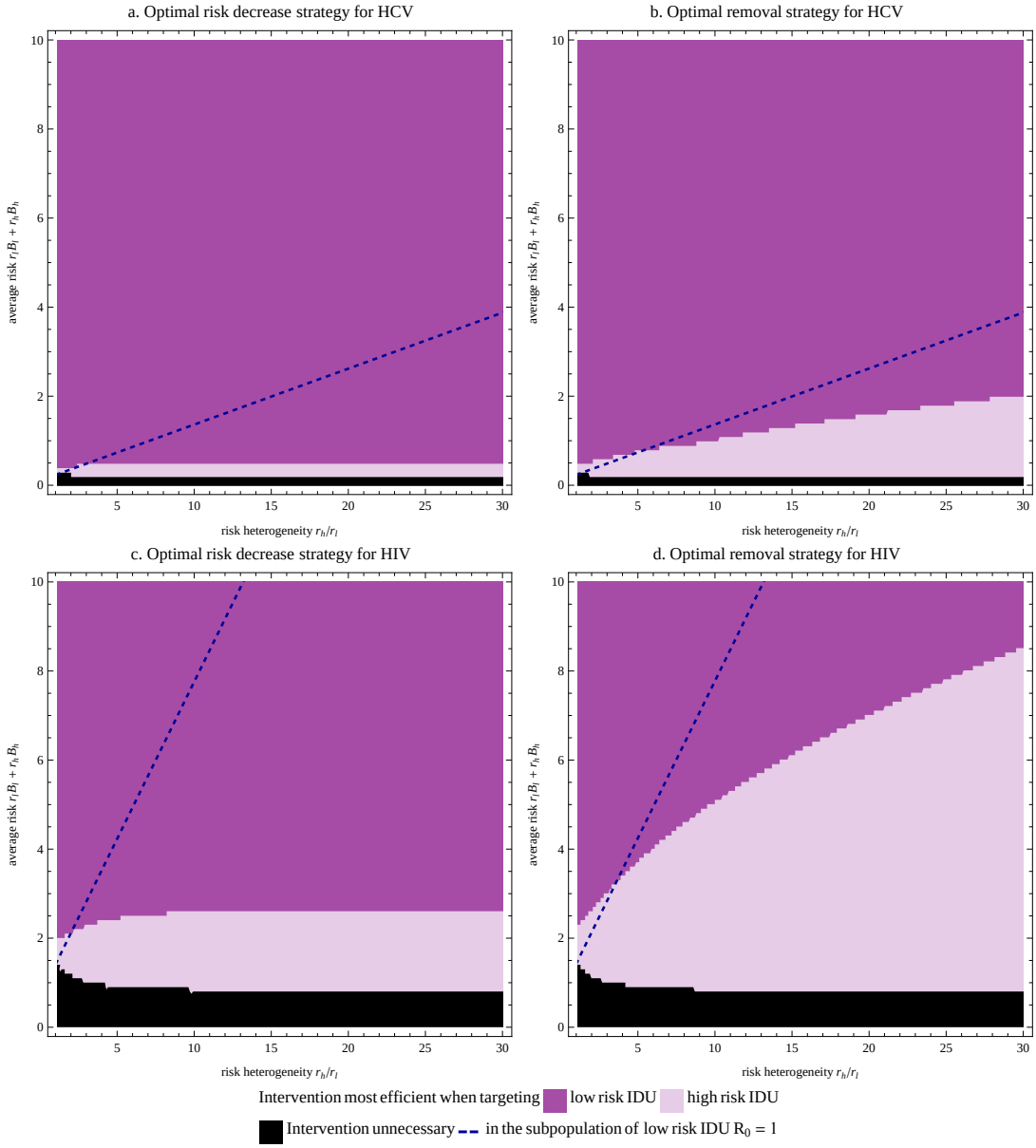
The level of mixing between subgroups will also impact the optimal intervention strategy (compare figure A2 with main text figure 4). With less sharing between subgroups, the probability of borrowing an infected syringe, m, becomes more different between the subgroups. In such a segregated situation, if $R_0 < 1$ in the subpopulation of only low risk IDU, intervention on low risk IDU may be of little use; low risk IDU are very unlikely to become infected even without intervention (compare especially figures A2d and 4d). On the other hand, if $R_0 > 1$ in the subpopulation of only low risk IDU, segregation between groups may make intervention on low risk IDU relatively more useful. The greater difference in m increases the difference in the probability of preventing primary infection between intervening on low and high risk IDU; removal of low risk IDU is much more likely to be on time, lowering of their risk is much more likely to truly prevent rather than merely delay infection.

Figure A1: The most efficient targeting strategy by relative size of the risk subgroups



Intervention efficiency is in terms of infections prevented per prevented borrowing act (figures a and c) or per IDU removal (figures b and d). For risk decrease intervention, the number of borrowing acts prevented per month $E_r = 50$. For removal intervention, the number of IDU removed per month $E_\mu = 2$. Lines end when all risk is prevented in the targeted subgroup (figures a and c) or when all IDU are removed from the targeted subgroup (figures b and d). Low risk IDU borrow and lend out $r_l = 0.65$ syringes per month, remaining IDU borrow and lend out $r_h = 4.76$ syringes per month. We assume proportionate mixing. Without intervention population size N is 1000. Remaining model parameters are as given in Table A1.

Figure A2: The most efficient targeting strategy when sharing occurs mostly within subgroups, $q = 0.9$



The most efficient intervention strategy (targeting low risk IDU or targeting high risk IDU) for different distributions of risk within the population, at little intervention effort (i.e. rate of removal intervention is 0.00001 IDU per month, risk decrease intervention is 0.0001 syringes per month). We assume two risk groups of equal size. Compared to figure 4 in the main text where we assumed proportionate mixing, we now assume sharing to be mostly within subgroups, $q = 0.9$. At low average risk infection does not spread, intervention is redundant. Below blue dashed lines intervention on high risk IDU only, at high enough intervention effort, has the potential of eradicating infection from the population. That is, risk of low risk IDU is too low to sustain spread of infection in a population of only low risk IDU ($R_0 < 1$). Remaining model parameters are as given in Table A1.

2 An intermediate level model

Here we study the influence of the disease infectiousness p on (targeted) intervention effects.

Methods

We consider the equations for the expected number of primary and secondary infections prevented, κ_p and κ_s respectively, in a population with two risk types and with disease at equilibrium. That is, the probability of borrowing an infected syringe m becomes a function of the risk of the two risk types. All other factors are neglected, we do not include an acute stage, clearing of disease, disease induced mortality, preferential within group mixing etc., or influence of intervention on prevalence, as in the full population model. With S and C we denote susceptible and infected individuals respectively, subscripts l and h denote low and high risk individuals respectively. Other variables are as defined for the individual level calculations in the main text. We have the following simple set of differential equations:

$$\begin{aligned}
\frac{dS_l}{dt} &= B_l - pr_l m S_l - \mu S_l \\
\frac{dC_l}{dt} &= pr_l m S_l - \mu S_l \\
\frac{dS_h}{dt} &= B_h - pr_h m S_h - \mu S_h \\
\frac{dC_h}{dt} &= pr_h m S_h - \mu S_h
\end{aligned}$$

with

$$m = \frac{r_l C_l + r_h C_h}{r_l(S_l + C_l) + r_h(S_h + C_h)}$$

By setting the left-hand sides of the differential equations to 0 we can solve for m explicitly. By also defining population risk and risk distribution, κ_p and κ_s only depend on the natural injecting cessation rate μ and disease infectiousness p.

Results

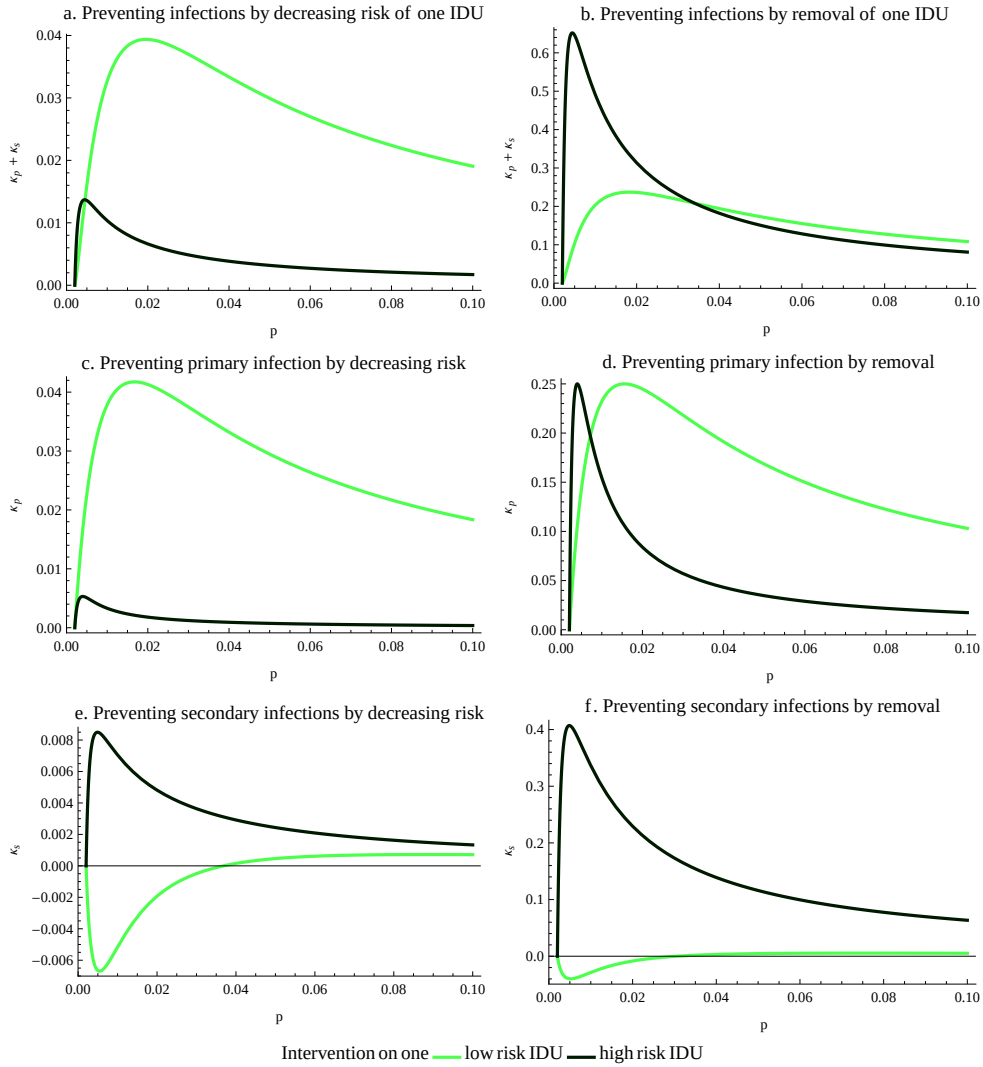
With this simplified model, we can more directly investigate the influence of disease infectiousness p on the effects of (targeted) intervention, in isolation from other particulars of disease (see figure A3). Removal of a high risk IDU prevents much more risk, resulting in much greater benefits in infections prevented, unless disease infectiousness is high (figure A3b). In the latter case, high risk IDU are likely already infected before they are reached by intervention. Intervention on a lower risk IDU then gives a much greater probability of preventing primary infection, which outweighs the smaller number of secondary infections prevented (figures A3d and A3f). Lowering risk prevention usually has much greater effects when one low risk individual is reached (figure A3a). Only at very low disease infectiousness do we find greater benefits from lowering risk of one high risk IDU, by prevention of secondary infections (figure A3c).

We additionally investigated (targeted) intervention effects at the population level as influenced solely by disease infectiousness p (see figure A4). The effects of the two types of intervention in this situation are remarkably similar to those found using the full population model (compare with figure 3 in the main text), despite ignoring complexities of HIV and HCV such as higher infectiousness for HIV in the acute infection phase, the possibility of clearing HCV, disease induced mortality and interaction between the two diseases.

We also considered the influence of population risk distribution on intervention effects directly from κ_p and κ_s (see figure A5). The qualitative picture of which group to target (high risk or low risk IDU) in order to prevent most infections is quite similar to that found using the full population model we introduced in our main text (compare with figure 4 in the main text). This also shows how disease infectivity is a main factor in determining the optimal intervention strategy.

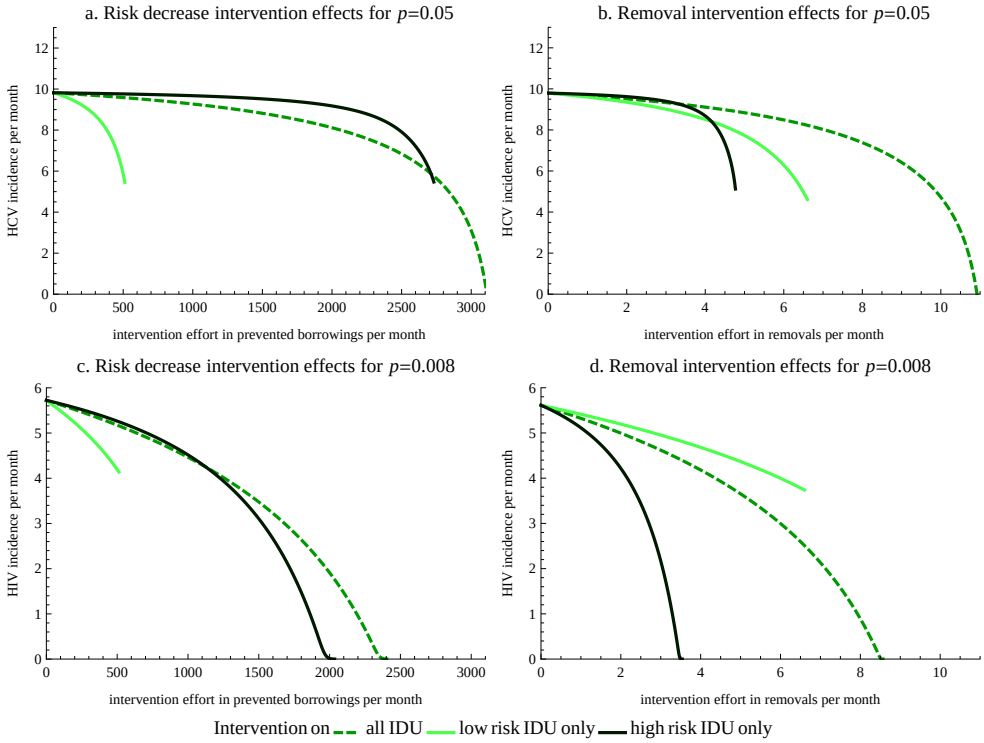
Additionally we note that in our full population model presence of HIV, by higher mortality among higher risk IDU, lowers HCV prevalence. However, this effect is very slight (in our baselines risk scenario, HCV incidence is decreased by less than 2% by presence of HIV), so that the effects of (targeted) intervention for HCV are almost unaltered in the absence of HIV (results not shown).

Figure A3: Intervention on a single individual as a function of disease infectiousness p



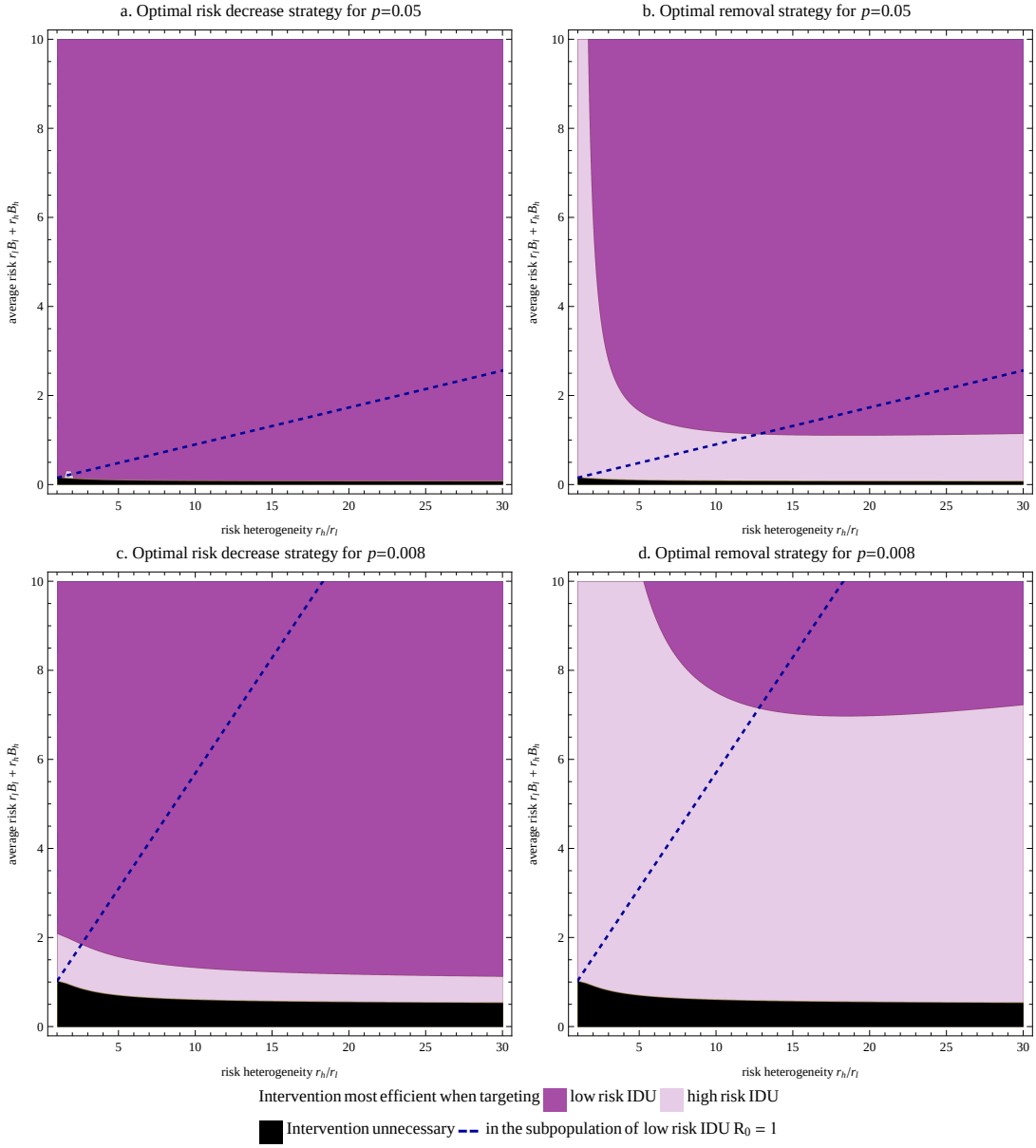
The expected benefits in infections prevented (primary κ_p and secondary κ_s) by intervention on one individual in a population consisting of two risk types, with disease prevalence at equilibrium. As for the more complicated population model, we assume that 58% of IDU are low risk, these share $r_l = 0.65$ syringes per month, high risk IDU share $r_h = 4.76$ syringes per month. Risk decrease intervention here lowers risk by $r_r = 0.1$ syringes per month.

Figure A4: Intervention on a heterogeneous population of IDU as influenced by disease infectiousness p



Effects of intervention on the incidence in a simple model for two types of intervention. This figure was created using the more complicated population level model, but setting $p^{H_A} = p^{H_C}, d = d^H = \mu^C = \mu^H = 0$. $p = 0.008$ accords with infectiousness of chronic HIV, $p = 0.05$ with the much higher infectiousness of HCV (compare with figure 3 in the main text). By risk decrease intervention random borrowing acts are prevented. By removal intervention random IDU are taken from the IDU population. Intervention is untargeted or targeted only at high or only at low risk IDU. Lines end when all risk is prevented in the targeted subgroup (figures a and c) or when all IDU are removed from the targeted subgroup (figures b and d). As for the more complicated population model, 58% of newly recruited IDU are low risk, without intervention these borrow and lend out 0.65 syringes per month, remaining IDU borrow and lend out 4.76 syringes per month. We assume proportionate mixing. Without intervention population size N is 1000. Remaining model parameters are as given in Table A1.

Figure A5: The most efficient targeting strategy by population risk distribution as influenced by disease infectiousness p



The most efficient intervention strategy (targeting low risk IDU or targeting high risk IDU) for different distributions of risk within the population, as calculated by comparing expected infections prevented (primary κ_p and secondary κ_s) one one high risk or one low risk IDU. For risk lowering intervention we set $r_r = 0.00000000001$ syringes per month, i.e. effort is minimal, comparable to figure 4 in the main text. $p = 0.008$ accords with infectiousness of chronic HIV, $p = 0.05$ with the much higher infectiousness of HCV. We assume two risk groups of equal size. At low average risk infection does not spread, intervention is redundant. Below blue dashed lines intervention on high risk IDU only, at high enough intervention effort, has the potential of eradicating infection from the population. That is, risk of low risk IDU is too low to sustain spread of infection in a population of only low risk IDU ($R_0 < 1$). Remaining model parameters are as given in Table A1.

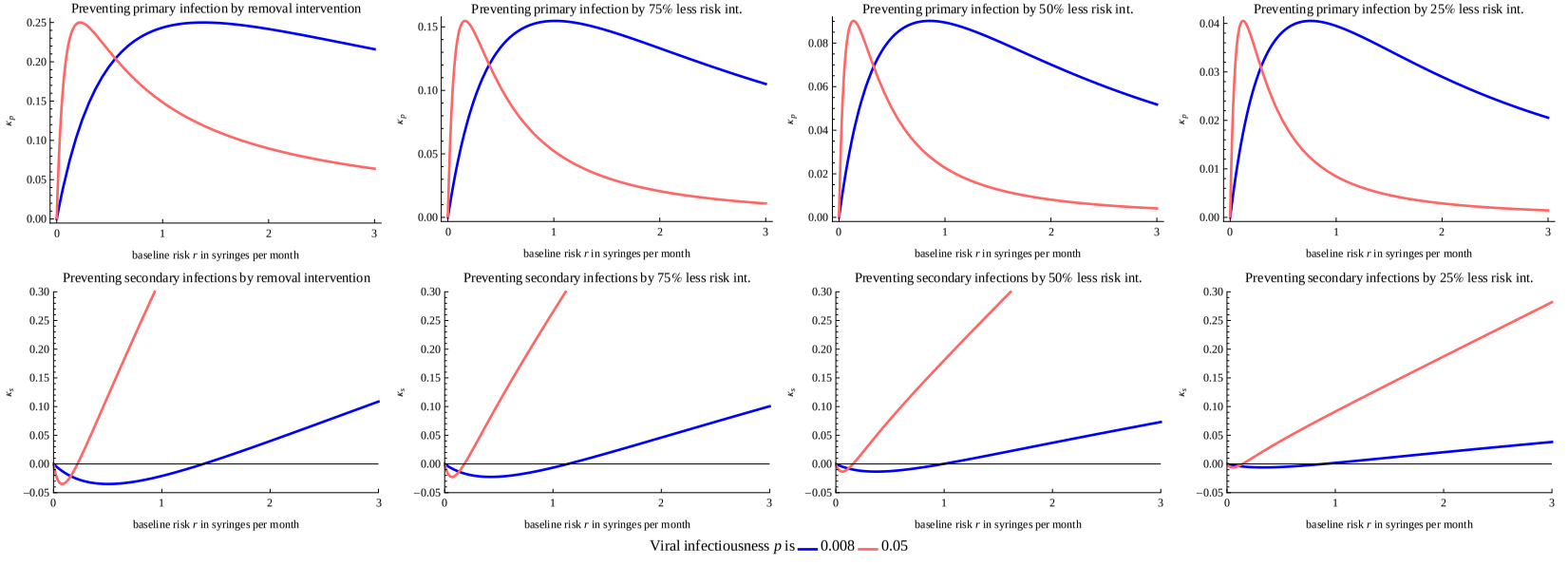
3 Incomplete removal prevention

Assuming that intervention can prevent all further risk of individuals is likely too optimistic. We investigate here the effects of incompletely removing individuals from the injecting population.

Methods

We extended our differential equations model with two additional risk subgroups. Rather than removal from the population (as in our main model), μ_E in this case described the rate at which individuals entered these new risk subgroups, in which individuals take a fraction of the risk taken in their original subgroup. As opposed to risk decrease intervention, this implies that intervention on higher risk IDU still prevents a greater absolute number of syringe exchanges. We only considered random mixing between all groups, $q = 0$, i.e. m did not need to be redefined.

Figure A6: Incomplete removal intervention on a single individual

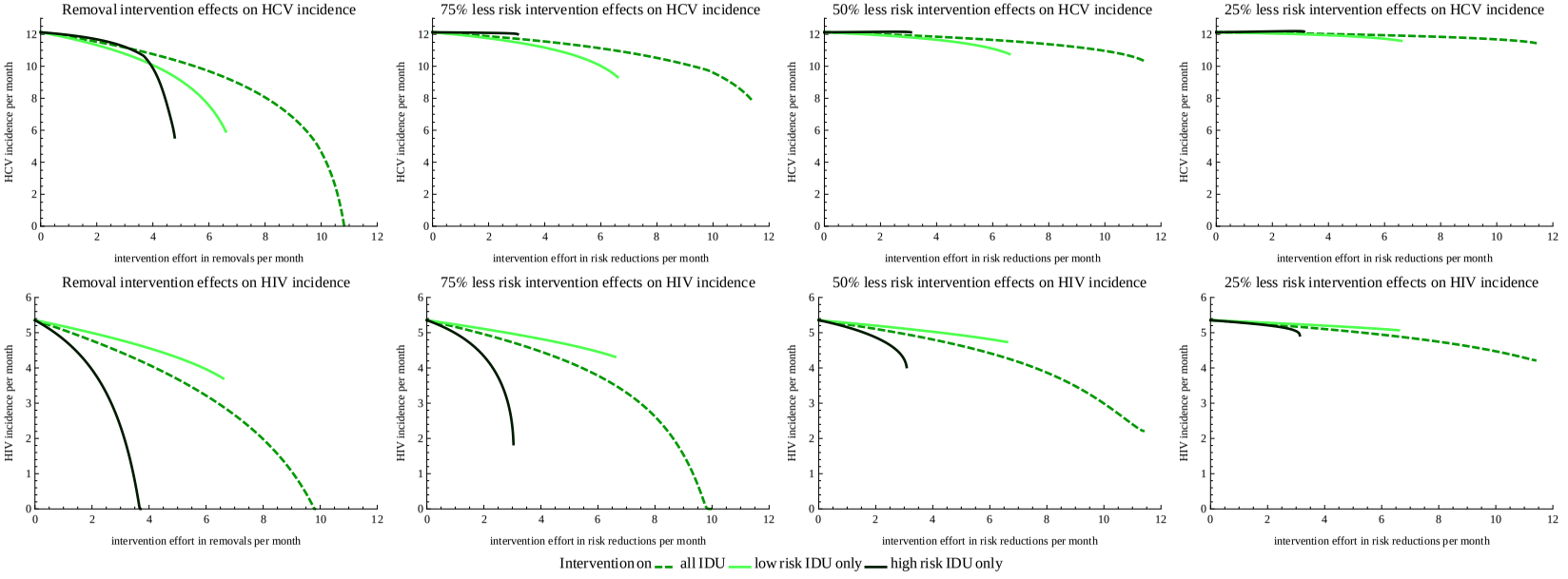


Probability of preventing a primary infection and the expected number of secondary infections prevented by intervention on a single individual (equations κ_p and κ_s respectively), shown for two levels of viral infectiousness p ($p = 0.008$ accords with infectiousness of chronic HIV, $p = 0.05$ with the much higher infectiousness of HCV). Columns from left to right: from intervention onwards we prevent all risk ($r_r = r$, same as for figures 2b and 2d in the main text), 75% of risk ($r_r = \frac{3}{4}r$), 50% of risk ($r_r = \frac{2}{4}r$), and 25% of risk ($r_r = \frac{1}{4}r$). Note that along the top row, the range of the y-axis varies greatly. $\mu = 0.0083$ per month, $m = 0.75$. $u = \frac{\mu}{\mu + rpm}$, i.e. an individual is removed at a random moment within their drug using career.

Results

Unsurprisingly, with incomplete risk reduction, the probability of preventing infections decreases (see figure A6). Especially the probability of preventing primary infection drops rapidly, and the individual risk r for which this probability has its peak is shifted slightly towards lower values. Implemented structurally at the population level, with 75% rather than 100% decrease in risk, HCV incidence reduction allready becomes minimal (see figure A7). For HIV, relevant incidence reduction may still be expected from intervention lowering high risk by only 50%. Which risk group to optimally target does not alter with the fraction of risk reduction.

Figure A7: Incomplete removal intervention on a heterogeneous population of IDU



Effects of incomplete removal intervention on the incidence of HIV and HCV. Columns from left to right: from intervention onwards we prevent all risk (same as figures 3b and 3d in the main text), 75% of risk, 50% of risk and 25% of risk. Intervention is untargeted or targeted only at high or only at low risk IDU. Lines end when all IDU are moved from the targeted subgroup to a lower risk subgroup. 58% of newly recruited IDU are low risk, without intervention these borrow and lend out 0.65 syringes per month, remaining IDU borrow and lend out 4.76 syringes per month. We assume proportionate mixing. Without intervention population size N is 1000. Remaining model parameters are as given in Table A1.

4 Switching risk behaviour

In our main article we assume individual risk behaviour to be stable over time. However, risk tendencies could be related to personal circumstances that may change, such as homelessness. In this Appendix chapter we discuss the effects that risk switching by (part of) the population has on the effects of the different types of intervention.

Methods

We modified the original model to incorporate that (a fraction of) individuals can switch between the two risk levels. As before, constantly low risk IDU are denoted by subscript l, and constantly high risk IDU by subscript h. We add two new subgroups sl and sh which consist of individuals also taking low and high risk respectively, but with rate w_l individuals may switch from subgroup sl to sh, and with rate w_h from sh to sl. For these subgroups we have recruitment rates B_{sl} and B_{sh} of new uninfected IDU. By setting $\frac{w_h}{w_l} = \frac{B_{sl}}{B_{sh}}$ we achieve that (without disease mortality) the relative high to low risk fraction is constant over injecting time (i.e. an average individual does not experience a changing force of infection over injecting time).

Probability m^C that a randomly borrowed syringe carries HCV infection now includes borrowing from all four groups, i.e.

$$m^C = (\mathfrak{r}_l f_l \pi_l + \mathfrak{r}_h f_h \pi_h + \mathfrak{r}_{sl} f_{sl} \pi_{sl} + \mathfrak{r}_{sh} f_{sh} \pi_{sh})/$$
$$(\mathfrak{r}_l f_l + \mathfrak{r}_h f_h + \mathfrak{r}_{sl} f_{sl} + \mathfrak{r}_{sh} f_{sh})$$

Similarly the probability that a randomly borrowed syringe carries HIV from acute infection becomes

$$m^{H_A} = (\mathfrak{r}_l f_l \pi_l^{H_A} + \mathfrak{r}_h f_h \pi_h^{H_A} + \mathfrak{r}_{sl} f_{sl} \pi_{sl}^{H_A} + \mathfrak{r}_{sh} f_{sh} \pi_{sh}^{H_A})/$$
$$(\mathfrak{r}_l f_l + \mathfrak{r}_h f_h + \mathfrak{r}_{sl} f_{sl} + \mathfrak{r}_{sh} f_{sh})$$

and that it carries HIV from chronic infection

$$m^{H_C} = (\mathfrak{r}_l f_l \pi_l^{H_C} + \mathfrak{r}_h f_h \pi_h^{H_C} + \mathfrak{r}_{sl} f_{sl} \pi_{sl}^{H_C} + \mathfrak{r}_{sh} f_{sh} \pi_{sh}^{H_C})/$$
$$(\mathfrak{r}_l f_l + \mathfrak{r}_h f_h + \mathfrak{r}_{sl} f_{sl} + \mathfrak{r}_{sh} f_{sh})$$

The model is extended by the following differential equations:

$$\begin{aligned}
\frac{dS^S_{sl}}{dt} &= B_{sl} + d\theta^C I^S_{sl} - S^S_{sl}(\mu + \lambda^C_{sl} + \lambda^H_{sl} + w_{sl}) + w_{sh} S^S_{sh} \\
\frac{dS^I_{sl}}{dt} &= \lambda^H_{sl} S^S_{sl} + d\theta^C I^I_{sl} - S^I_{sl}(\mu + \lambda^C_{sl} + \theta^H + w_{sl}) + w_{sh} S^I_{sh} \\
\frac{dS^C_{sl}}{dt} &= \theta^H S^I_{sl} + d^H \theta^C I^C_{sl} - S^C_{sl}(\mu + \mu^H + \lambda^C_{sl} + w_{sl}) + w_{sh} S^C_{sh} \\
\frac{dI^S_{sl}}{dt} &= \lambda^C_{sl} S^S_{sl} - I^S_{sl}(\mu + \lambda^H_{sl} + \theta^C + w_{sl}) + w_{sh} I^S_{sh} \\
\frac{dI^I_{sl}}{dt} &= \lambda^C_{sl} S^I_{sl} + \lambda^H_{sl} I^S_{sl} - I^I_{sl}(\mu + \theta^C + \theta^H + w_{sl}) + w_{sh} I^I_{sh} \\
\frac{dI^C_{sl}}{dt} &= \lambda^C_{sl} S^C_{sl} + \theta^H I^I_{sl} - I^C_{sl}(\mu + \mu^H + \theta^C + w_{sl}) + w_{sh} I^C_{sh} \\
\frac{dC^S_{sl}}{dt} &= (1-d)\theta^C I^S_{sl} - C^S_{sl}(\mu + \mu^C + \lambda^H_{sl} + w_{sl}) + w_{sh} C^S_{sh} \\
\frac{dC^I_{sl}}{dt} &= (1-d)\theta^C I^I_{sl} + \lambda^H_{sl} C^S_{sl} - C^I_{sl}(\mu + \mu^C + \theta^H + w_{sl}) + w_{sh} C^I_{sh} \\
\frac{dC^C_{sl}}{dt} &= (1-d^H)\theta^C I^C_{sl} + \theta^H C^I_{sl} - C^C_{sl}(\mu + \mu^C + \mu^H + w_{sl}) + w_{sh} C^C_{sh} \\
\frac{dS^S_{sh}}{dt} &= B_{sh} + d\theta^C I^S_{sh} - S^S_{sh}(\mu + \lambda^C_{sh} + \lambda^H_{sh} + w_{sh}) + w_{sl} S^S_{sl} \\
\frac{dS^I_{sh}}{dt} &= \lambda^H_{sh} S^S_{sh} + d\theta^C I^I_{sh} - S^I_{sh}(\mu + \lambda^C_{sh} + \theta^H + w_{sh}) + w_{sl} S^I_{sl} \\
\frac{dS^C_{sh}}{dt} &= \theta^H S^I_{sh} + d^{sl}\theta^C I^C_{sh} - S^C_{sh}(\mu + \mu^{sl} + \lambda^C_{sh} + w_{sh}) + w_{sl} S^C_{sl} \\
\frac{dI^S_{sh}}{dt} &= \lambda^C_{sh} S^S_{sh} - I^S_{sh}(\mu + \lambda^H_{sh} + \theta^C + w_{sh}) + w_{sl} I^S_{sl} \\
\frac{dI^I_{sh}}{dt} &= \lambda^C_{sh} S^I_{sh} + \lambda^H_{sh} I^S_{sh} - I^I_{sh}(\mu + \theta^C + \theta^H + w_{sh}) + w_{sl} I^I_{sl} \\
\frac{dI^C_{sh}}{dt} &= \lambda^C_{sh} S^C_{sh} + \theta^H I^I_{sh} - I^C_{sh}(\mu + \mu^{sl} + \theta^C + w_{sh}) + w_{sl} I^C_{sl} \\
\frac{dC^S_{sh}}{dt} &= (1-d)\theta^C I^S_{sh} - C^S_{sh}(\mu + \mu^C + \lambda^H_{sh} + w_{sh}) + w_{sl} C^S_{sl} \\
\frac{dC^I_{sh}}{dt} &= (1-d)\theta^C I^I_{sh} + \lambda^H_{sh} C^S_{sh} - C^I_{sh}(\mu + \mu^C + \theta^H + w_{sh}) + w_{sl} C^I_{sl} \\
\frac{dC^C_{sh}}{dt} &= (1-d^{sl})\theta^C I^C_{sh} + \theta^H C^I_{sh} - C^C_{sh}(\mu + \mu^C + \mu^{sl} + w_{sh}) + w_{sl} C^C_{sl}
\end{aligned}$$

Results

Equilibrium HIV and HCV prevalence in a population with risk switching IDU We have shown before that heterogeneity in risk affects the equilibrium prevalence of HIV and HCV (de Vos et al 2012, repeated here in figures A8a and A8b). With more heterogeneity the disease can persist at lower average risk, but reaches lower prevalence compared to within a homogeneous population at higher average risk. This effect is even stronger with syringe borrowing more concentrated within risk subgroups, higher q, which causes prevalence to become more different between the risk subgroups.

Equilibrium HIV and HCV prevalence in a population with risk switching IDU We have shown before that heterogeneity in risk affects the equilibrium prevalence of HIV and HCV (de Vos et al 2012, repeated here in figures A8a and A8b). With more heterogeneity the disease can persist at lower average risk, but reaches lower prevalence compared to within a homogeneous population at higher average risk. This effect is even stronger with syringe borrowing more concentrated within risk subgroups, higher q, which causes prevalence to become more different between the risk subgroups.

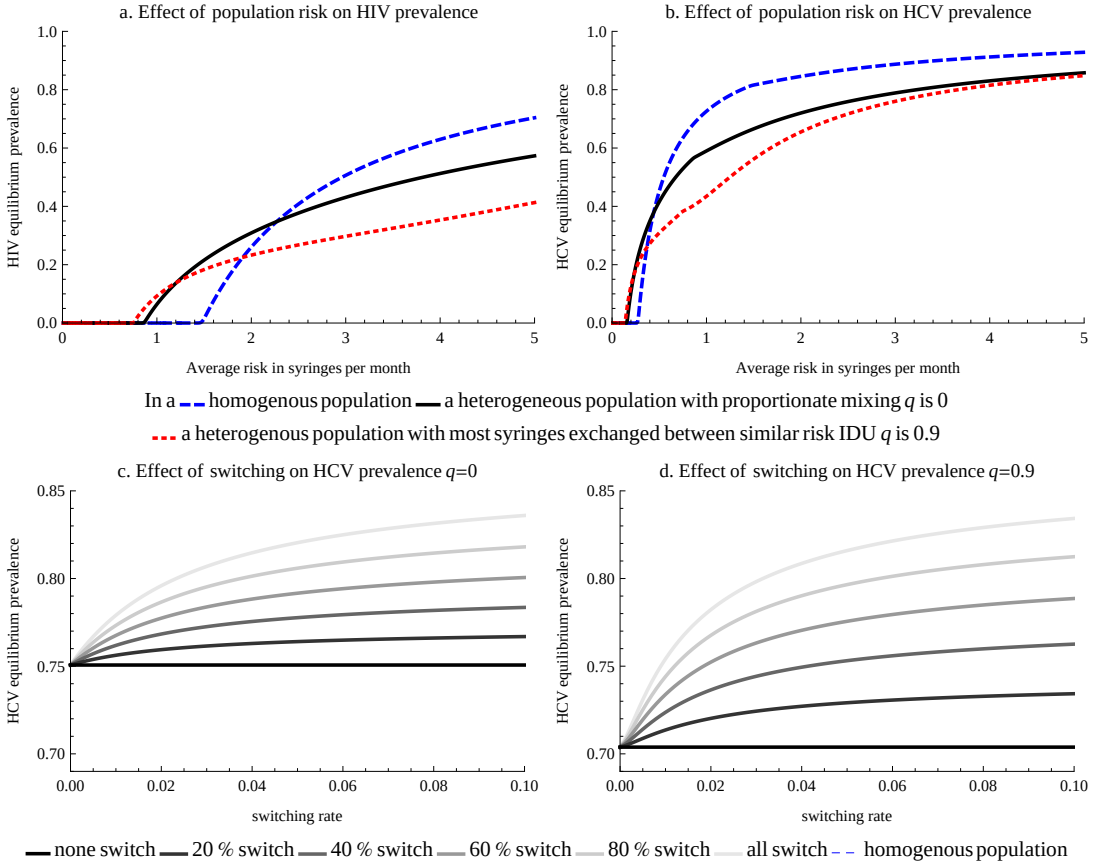
However, if risk types are not stable, the effect of heterogeneity on disease prevalence soon disappears (see figures A8c and A8d). We see that with sufficient switching, already at 0.05 switches per month (low risk IDU switching on average once per 20

months), the heterogeneous prevalences become near equal to the homogeneous prevalences. With proportionate mixing the influence of switching is simply proportional to the part of IDU that switch. With more within group mixing, switching of only part of the population has a relatively larger impact (figure A8c). As switching individuals make the groups more equal in prevalence it becomes irrelevant whether borrowing is within or between risk sub-groups.

Intervention when risk switching occurs As expected, with risk switching, it matters much less if intervention is targeted, because the probability to become infected averages out over high and low risk periods for IDU. Even though distributing syringes among lower risk IDU is still most efficient in preventing HCV in the risk switching scenario, this strategy now has even more limited results (figure A9). For removal intervention, with sufficient risk switching, all IDU are eventually reached even if we focus our effort on one risk type only, but benefits of such targeted intervention disappears as well (figure A10).

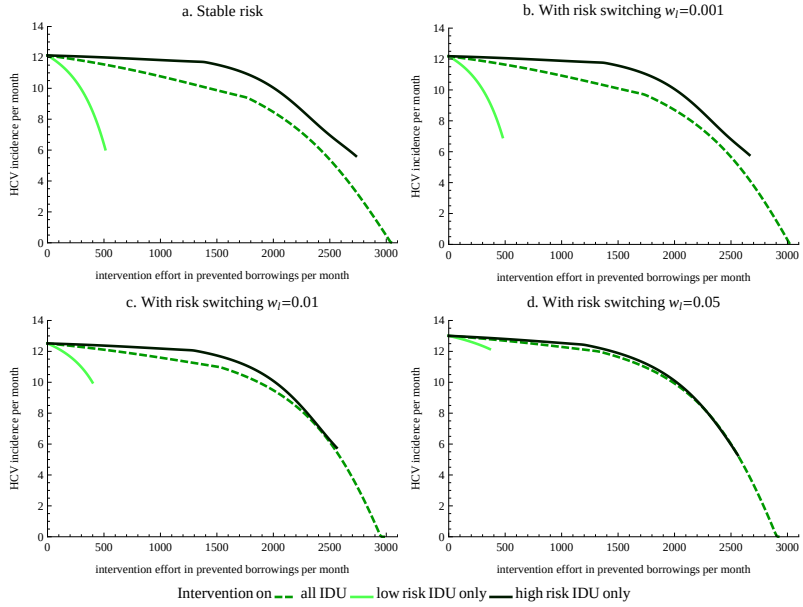
We conclude that when all IDU are prone to switching their risk behaviour, at about once per twenty months or more often, risk heterogeneity can in effect be ignored for intervention.

Figure A8: HIV and HCV equilibrium prevalence as influenced by average risk and risk heterogeneity



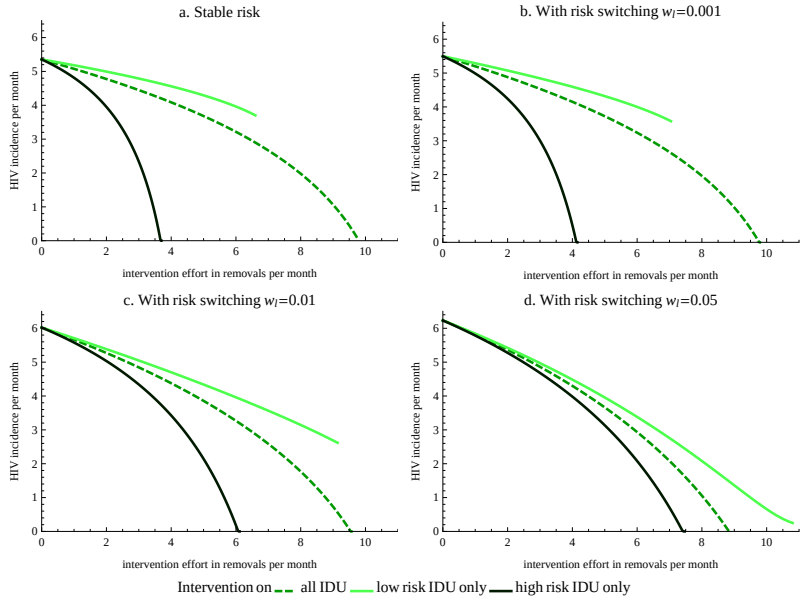
At recruitment 58% of IDU are low risk. For figures A and B, for the heterogeneous populations high to low risk is held constant at 4.76/0.65. For figures C and D $r_l = 0.65$ and $r_h = 4.76$, and the fraction of newly recruited IDU prone to switching, $(B_{sh} + B_{sl})/(B_h + B_l + B_{sh} + B_{sl})$ is given in the legend. Since recruitment of low risk IDU is higher, high risk IDU switch somewhat faster, $w_h = \frac{B_{sl}}{B_{sh}} w_l$, so that without disease mortality average risk would stay similar over individual injecting time. Remaining model parameters are as given in Table A1.

Figure A9: Risk decrease intervention effects on HCV incidence when individuals switch between risk levels



By risk decrease intervention random borrowing acts are prevented. Lines end when all risk is prevented in the targeted subgroup. At recruitment 58% of IDU are low risk, these borrow and lend out $r_l = 0.65$ syringes per month, remaining IDU borrow and lend out $r_h = 4.76$ syringes per month. We assume proportionate mixing. All low risk IDU switch to high risk at rate w_l, $w_h = \frac{B_{sl}}{B_{sh}} w_l$. Without intervention population size N is 1000. Remaining model parameters are as given in Table A1.

Figure A10: Removal intervention effects on HIV incidence when individuals switch between risk levels



By removal intervention random IDU are taken from the IDU population. Lines end when all IDU are removed from the targeted subgroup. At recruitment 58% of IDU are low risk, these borrow and lend out $r_l = 0.65$ syringes per month, remaining IDU borrow and lend out $r_h = 4.76$ syringes per month. We assume proportionate mixing. All low risk IDU switch to high risk at rate w_l, $w_h = \frac{B_{sl}}{B_{sh}} w_l$. Without intervention population size N is 1000. Remaining model parameters are as given in Table A1.

CHAPTER 6

Benefits of Hepatitis C Virus treatment: a balance of preventing onwards transmission and re-infection

Benefits of Hepatitis C Virus treatment: a balance of preventing onwards transmission and re-infection

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Abstract

By treating HCV-infected Injecting Drug Users (IDUs), we may prevent infections to other IDUs. Curing preferentially individuals who most often share injecting equipment has the advantage of preventing more infections. However, such high risk behaviour IDUs are also more likely to become re-infected. We have created a model that can inform as to most efficient HCV treatment policy; the expected benefits per treatment of one HCV-infected IDU are calculated, defined as a decrease in the number of chronic HCV infections. This includes the probability that the cured IDU remains uninfected, and the number of new infections prevented both directly and indirectly in further infection generations. We explore analytically how these benefits depend on the syringe sharing frequency of the cured IDU.

We find that whom to best cure is determined by the prevalence of HCV contamination among exchanged syringes within the IDU population. Treating lowest risk IDUs is most beneficial above a certain prevalence of contamination, since the term for re-infection dominates the equation in this domain. At lower prevalence treating highest risk IDUs is most beneficial, since here the term for prevention dominates. In a much simplified model the threshold between domains is found at exactly 50% HCV prevalence. The threshold value is lowered when taking HCV induced mortality or increased infectiousness during an acute stage of infection into account. It is increased when taking into account treatment duration, or when HCV-treatment is combined with intervention that reduces the syringe sharing rate of the cured IDU.

Keywords: Hepatitis C Virus; injecting drugs; treatment as prevention; mathematical modelling; epidemiology

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1. Introduction

By sharing of contaminated needles and syringes, blood-borne infections are spread among injecting drug users (IDUs). Especially transmission of Hepatitis C Virus (HCV) via this route is likely: 50% to 90% prevalence within IDU populations is common [1]. In order to prevent the severe liver disease that can result from long term HCV infection, infected individuals may be cured by use of antiviral treatment [2]. Additional motivation for treatment is that it may prevent transmission of HCV to other IDUs, a concept known as treatment as prevention [3].

In this light, models have been set up to project the expected impact of HCV treatment of IDUs, taking herd immunity effects into account. Such studies explored the impact of differing levels of HCV treatment coverage, for specific settings and within specified time-windows, on HCV prevalence [4, 5, 6, 7] or HCV related costs [8]. It has been noted that the benefits of treatment may be impacted by who are treated; ex-IDUs or current IDUs [8], those who are or those who are not not also on methadone maintenance therapy [9, 10].

The potential for preventing infections to other IDUs is greatest when curing individuals who often share their injecting equipment, i.e. high risk IDUs. However, such IDUs also have a greater probability of becoming re-infected with HCV, which limits the benefits of their treatment both for themselves and for the population.

Here we aim to answer more in general as to which IDUs are best targeted for HCV treatment, from a public health perspective. We calculated the benefits per treated IDU, defined as the expected decrease in the number of chronic infections within the IDU population. Both the risk for re-infection and the potential for preventing onwards infection are captured in this single measure. This allowed us to explore explicitly how these benefits depend on the risk level of the treated IDU, in combination with other variables such as HCV prevalence.

2. Methods for obtaining the benefits

2.1. The model

Our model describes the expected time spent within different states of HCV infection (uninfected, acutely infected, chronically infected, under treatment) for an IDU, as influenced by treatment for HCV (see Figure 1). Within a first period of acute infection, individuals may clear HCV naturally. Only with long term chronic infection is individual health seriously compromised. Therefore we calculate the benefits of treating one chronically HCV infected IDU, B, defined as a reduction in the number of chronic HCV infections that would have otherwise occurred at any point in time, over the complete transmission chain.

For this calculation we assume equilibrium conditions, that is we consider a population with a stable HCV prevalence, as well as a stable distribution of risk behaviour (frequency of sharing syringes) of IDUs. Here we focus on the curing of one individual in an infinitely large population, i.e. curing of this one IDU does not change the fractions infected with HCV.

We distinguish between direct (section 3.1) and indirect (section 3.2) benefits of curing. The direct effects consist of the probability for the treated IDU (the index) to become cured, minus their probability for chronic re-infection. We also include in the direct effects the prevention of b_0 secondary infections otherwise produced by the index. In a first step for calculating the indirect effects of curing, we consider one IDU who is not infected by the index as a consequence of curing. The benefits of preventing this secondary case may be undone when this IDU acquires chronic infection from sharing syringes with other IDUs. By preventing this IDU from being infected by the index, however, we also prevent a number $\tilde{b}_o$ of onward infections further down the transmission chain.

The direct effects of curing can be calculated knowing only the risk of the cured index. The indirect effects depend on the syringe sharing frequency of those not being infected, which in turn depends on the population risk distribution. In section 3.4, for the simplifying case of a homogeneous population, we derive an explicit formula for the total benefits B.

In section 3.5 we show the existence of a threshold in viral prevalence, which fully determines who should be treated to maximise B. In section 3.6 we take into account treatment duration and the treatment success rate. In section 3.7 we extend the model with HCV induced mortality and behavioural change by intervention.

2.2. Definitions

In our calculations, notation is as follows: r is the risk of the treated index IDU, in syringes borrowed and lent out to other IDUs each month. Of syringes borrowed by the index, a proportion m_a carry acute infection, a proportion m_c carry chronic infection. These proportions follow from the prevalence among IDUs. When the index borrows at random,

$$m_a = \frac{\sum_{\hat{r}=0}^{\infty} f_{\hat{r}} \hat{r} A_{\hat{r}}}{\sum_{\hat{r}=0}^{\infty} f_{\hat{r}} \hat{r}} \text{ and } m_c = \frac{\sum_{\hat{r}=0}^{\infty} f_{\hat{r}} \hat{r} C_{\hat{r}}}{\sum_{\hat{r}=0}^{\infty} f_{\hat{r}} \hat{r}},$$

with $f_{\hat{r}}$ representing the number of IDUs with risk $\hat{r}$, and $A_{\hat{r}}$ and $C_{\hat{r}}$ respectively the acute and chronic HCV prevalence among these IDUs. We define total prevalence among syringes $m = m_a + m_c$. As we assume all IDUs to borrow and lend out syringes equally, m_a and m_c describe also the probabilities for an IDU borrowing a syringe to be acutely or chronically infected respectively. Therefore, a proportion $1 - m$ of those borrowing syringes from the index will be uninfected.

We define p_c, the probability of becoming infected when using a syringe contaminated by a chronically infected IDU, and p_a, the same when using a syringe previously used by an acutely infected IDU. Individuals move out of the acute HCV phase with rate θ, where d gives the proportion of these infections being cleared and $1 - d$ the proportion of infections leading to chronic HCV. μ is the death or stop injecting rate, μ_c the additional death rate experienced by chronically HCV infected IDUs.

Treatment lasts a fixed time, v, in months. Immediately upon starting treatment the IDU is no longer infectious, but during treatment the IDU cannot be re-infected. With s we denote the probability that treatment is successful in clearing HCV. We explore the effects of treating the index once.

The model is represented in Figure 1. Numerical results were obtained using Mathematica version 7. Parameter values are given in Table 1. These parameter values were based on published literature, as previously described and used in [11].

3. Calculation of the benefits

3.1. Direct benefits

For clarity of the model exposition, we first assume treatment to be instantaneous and always successful, i.e. $v = 0$ and $s = 1$, and we set $\mu_c = 0$, HCV infection does not cause mortality.

To compute the number of infections prevented, we need to know the impact of curing on the time individuals spend in the different states: uninfected u, acutely infected a and chronically infected c respectively. Individuals move through these different states as shown in Figure 1. Starting uninfected an individual can become infected, yet come back into the uninfected state after clearing an acute infection. We denote the probability for this to happen by g and we get

$$g = \frac{\lambda}{\lambda+\mu}\frac{d\theta}{\theta+\mu}.$$

Here the force of infection λ is assumed to be constant and given by $\lambda = r(p_a m_a + p_c m_c)$. The process of re-infection and clearing can occur an unlimited number of times. The expected number of times the uninfected state is reached for an individual starting uninfected is

$$\sum_{i=0}^{i=\infty} g^i = \frac{1}{1-g}.$$

We denote by T_{ij} the time spent in state j when starting in state i with $i, j = u, a, c$. We get

$$\begin{aligned}
T_{uu} &= \frac{1}{\lambda+\mu}\frac{1}{1-g} \\
T_{ua} &= \frac{1}{\theta+\mu}\frac{\lambda}{\lambda+\mu}\frac{1}{1-g} = \frac{\lambda}{\theta+\mu}T_{uu} \\
T_{uc} &= \frac{1}{\mu}\frac{(1-d)\theta}{\theta+\mu}\frac{\lambda}{\lambda+\mu}\frac{1}{1-g} = \frac{(1-d)\theta}{\theta+\mu}\frac{\lambda}{\mu}T_{uu} \\
T_{au} &= \frac{d\theta}{\theta+\mu}T_{uu} \\
T_{aa} &= \frac{1}{\theta+\mu} + \frac{d\theta}{\theta+\mu}T_{ua} \\
T_{ac} &= \frac{1}{\mu}\frac{(1-d)\theta}{\theta+\mu} + \frac{d\theta}{\theta+\mu}T_{uc} \\
T_{cc} &= \frac{1}{\mu} = T_{uu} + T_{ua} + T_{uc} = T_{au} + T_{aa} + T_{ac}.
\end{aligned}$$

Due to the Markov property of the model, the number of infections an individual in a given state will cause is simply proportional to the expected remaining life-time spend in the acute and chronic states. To compute the number of secondary infections prevented by curing the index, we subtract the number of infections caused by an individual who is not yet (but may become) infected from the number of infections caused by a chronically infected individual:

$$b_o = r(1-m)(p_c T_{cc} - (p_a T_{ua} + p_c T_{uc})).$$

For computing the benefits we are only interested in those infections that would have become chronic, since those that are cleared cause no disease. The probability of an infection to become chronic is given by

$$c = \frac{(1-d)\theta}{\theta+\mu}.$$

Due to curing the index will not be chronically infected for a fraction of his remaining injecting lifetime

$$(T_{cc} - T_{uc})\mu = 1 - \frac{(1-d)\theta}{\theta+\mu}\frac{\lambda}{\lambda+\mu}\frac{1}{1-g} = 1 - c\lambda T_{uu}.$$

In other words, we lower the number of chronic infections by 1, but chronic re-infection cancels out this benefit with probability $c\frac{\lambda}{\lambda+\mu}\frac{1}{1-g} = c\lambda T_{uu}$. We now define the direct benefits of curing b_d as:

$$b_d = 1 - c\lambda T_{uu} + c b_o.$$

3.2. Indirect benefits

We first consider one individual who was not infected due to the index not being infectious, and who shares syringes with frequency $\tilde{r}$. The number of infections $\tilde{b_o}$ that are prevented by this, within one further infection generation, is obtained by subtracting the number of infections caused by an IDU starting in the uninfected state from infections caused if this IDU were acutely infected:

$$\tilde{b_o} = \tilde{r}(1-m)(p_a T_{aa} + p_c T_{ac} - (p_a T_{ua} + p_c T_{uc}))$$

with risk r substituted by risk $\tilde{r}$ within λ in T_{ij}.

When not infected by the index, an IDU may still become chronically infected by borrowing syringes from other IDUs. The fraction lifetime with chronic infection prevented due to not becoming infected by the index is given by:

$$\begin{aligned}&(T_{ac} - T_{uc})\mu \\ &= \frac{(1-d)\theta}{\theta+\mu}\frac{1}{1-g} - \frac{(1-d)\theta}{\theta+\mu}\frac{\lambda}{\lambda+\mu}\frac{1}{1-g} \\ &= c - c\lambda(T_{uu} - T_{au}),\end{aligned}$$

again with r replaced by $\tilde{r}$ within λ in T_{ij}. The above describes the probability that by not being infected by the index, chronic infection is averted for the remaining lifetime, rather than merely delayed. Infection would have turned chronic with probability c. By not being infected by the index, the individual will be at risk for obtaining chronic infection from others for an additional time $T_{uu} - T_{au}$.

We define the indirect benefits of one IDU not being infected $\tilde{b_d}$:

$$\tilde{b_d} = -c\lambda(T_{uu} - T_{au}) + c\tilde{b_o},$$

where in λ and in T_{ij}, $\tilde{r}$ replaces r. Note that while the probability of acquiring chronic infection from others is included here, prevention of chronic infection acquired from the index was already accounted for in b_d, and is therefore not repeated here. Again we only count as beneficial those prevented infections that would have turned chronic.

3.3. A homogeneous population at equilibrium

To obtain the full benefits B of curing one IDU, we need to account for the benefits $\tilde{b_d}$ from any IDU not infected due to curing of the index, over all further infection generations. These will depend on the risk of the IDUs that borrow from the index, and the risk of those borrowing from these IDUs in turn, etc. To enable full calculation of B therefore, we need to fully define the population risk structure. To demonstrate the method, we consider here the simplest situation, that is we assume a homogeneous population with all IDUs except the treated index engaging in risk $\tilde{r}$. With U, A and C representing numbers of uninfected, acutely and chronically infected IDUs respectively, population change is described by:

$$\begin{aligned}\frac{dU}{dt} &= \mu(U+A+C) - \lambda U + d\theta A - \mu U \\ \frac{dA}{dt} &= +\lambda U - \theta A - \mu A \\ \frac{dC}{dt} &= (1-d)\theta A - \mu C\end{aligned}$$

with

$$\lambda = \tilde{r}p_a\frac{A}{U+A+C} + \tilde{r}p_c\frac{C}{U+A+C}.$$

Setting the above differential equations to 0, we find that in equilibrium

$$\begin{aligned}m_a &= \frac{A}{U+A+C} = \frac{\mu(\tilde{r}(p_a\mu + p_c(1-d)\theta) - \mu\theta - \mu^2)}{\tilde{r}(p_a\mu + p_c(1-d)\theta)(\mu + (1-d)\theta)} \\ m_c &= \frac{C}{U+A+C} = \frac{(1-d)\theta}{\mu}m_a \\ m &= m_a + m_c = 1 - \frac{\mu(\mu+\theta)}{\tilde{r}(p_a\mu + p_c(1-d)\theta)}.\end{aligned}$$

Note that in this homogeneous population only, HCV prevalence among syringes equals HCV prevalence among IDUs. From this equation for m at equilibrium we derive $\tilde{r}$ (see Figure 2). This allows us to derive the total benefits B, as shown below.

3.4. The full benefits

We designate the IDUs whose infection by the index has been prevented as generation 1; furthermore we denote IDUs whose infection by an individual in generation i has been prevented as generation $i+1$ for all $i \geq 1$. The number of IDUs in each generation hence equals $b_o\tilde{b_o}^{i-1}$. Multiplying this by the indirect benefits per prevented case, $\tilde{b_d}$, we obtain the indirect benefits per generation. The sum of these indirect benefits over all generations, together with the direct benefits, gives us the full benefits:

$$B = b_d + b_o\tilde{b_d}\sum_{i=1}^{i=\infty}\tilde{b_o}^{i-1} = b_d + b_o\tilde{b_d}\frac{1}{1-\tilde{b_o}}.$$

Using the above equilibrium conditions on m_a and m_c for the homogeneous population, we find that $\tilde{b_o} = 1 - m$, equal to the fraction of uninfected syringes (or IDUs). This is clearly < 1 when HCV is present in the population, ensuring convergence of the total benefits B. In Figure 2 we show b_d and B for a fully homogeneous population, in Figure 3 we vary risk of the treated index.

B remains bounded also for any risk heterogeneous population at equilibrium, even though for highest risk IDUs possibly $\tilde{b}_o > 1$. In the endemic steady state, an average newly infected individual causes on average one new infection before clearing infection or dying. Given also the possibility, when not infected through transmission from the index, for infection by others instead, $\tilde{b}_o$ for the average prevented case must be < 1.

Note that since our formulae presume a stable HCV prevalence, outside of equilibrium conditions our calculations are not valid. For example, with lower than equilibrium prevalence, an average $\tilde{b}_o > 1$ is likely. In this case, for proper calculation of B, we should incorporate how $\tilde{b}_o$ decreases over time as prevalence increases towards the equilibrium. Therefore, at lower than equilibrium prevalence, our calculation of B (ignoring prevalence change) would actually represent an overestimate and upper bound of the total decrease in the number of chronic HCV infections resulting from curing one IDU.

3.5. A threshold determining whom to treat

When chronic and acute infectiousness are equal, $p_a = p_c = p$, the direct benefits b_d simplify to:

$$b_d = crpT_{uu}(1 - 2m) + 1.$$

We see that $b_d = 1$ for $m = 0.5$ regardless of r. rpT_{uu} is monotonically increasing with risk r so that we can conclude that for $m < 0.5$ b_d is an increasing function of r. That is, if we wish to maximise the direct benefits we target treatment to those with highest risk. Conversely, for $m > 0.5$ risk of re-infection outweighs the potential to prevent infection to others, we find that curing of those with lowest risk will result in largest benefit.

The indirect benefits per IDU not infected due to the index not being infectious also simplify:

$$\tilde{b_d} = c\tilde{r}p(T_{uu} - T_{au})(1 - 2m).$$

with r replaced by $\tilde{r}$ within λ in T_{uu} and T_{au}. Regardless of risk $\tilde{r}$ of the IDU not infected, $\tilde{b_d} = 0$ for $m = 0.5$. Also $\tilde{b_d}$ will be positive only when $m < 0.5$, and negative when $m > 0.5$. That is, the direct effects of curing b_d are an overestimation of the full effects of curing B at $m > 0.5$, and an underestimation at $m < 0.5$. We conclude that also when taking further infection generations into account, the threshold at $m = 0.5$ fully determines which IDUs are best treated.

Note that we did not need to fully derive B in order to show this threshold effect. That is, with $p_a = p_c = p$, who to best treat depends fully on prevalence among syringes m, and only indirectly (as m depends on it) on the population risk structure. The threshold value in m is affected when we do not assume equal infectiousness over the acute and chronic infection states (compare Figures 3 and 4).

3.6. Treatment duration and treatment failure

Here we include that treatment lasts a number of months v. Immediately upon starting treatment the IDU is no longer infectious, and during treatment the IDU cannot be re-infected. Treatment is successful with probability s. In case of treatment failure, the index reverts to the chronic infection state.

The probability for surviving treatment and becoming cured is $se^{-\mu v}$. The probability for surviving treatment but not becoming cured is $(1-s)e^{-\mu v}$. For the number of infections prevented we now find:

$$\begin{aligned} b_o &= r(1-m) \\ &\quad (p_cT_{cc} - (1-s)e^{-\mu v}p_cT_{cc} - se^{-\mu v}(p_aT_{ua} + p_cT_{uc})). \end{aligned}$$

In the benefits we count only successful curing of the index, and only after curing re-infection can occur, so that the direct benefits b_d become:

$$b_d = se^{-\mu v}\,(1 - c\lambda T_{uu}) + cb_o.$$

Note that when treatment fails it may still result in benefits, by prevention of infections during the time of treatment. However, when treatment is instantaneous ($v = 0$), the number of infections prevented b_o, and also the direct benefits b_d and the full benefits B, become simply linearly increasing with the treatment success rate s. In that case, s does not affect the threshold discussed in section 3.5. In Figure 5 we show numerical results for the influence of treatment duration v.

3.7. HCV induced mortality and behavioural change

Here we determine the benefits from combining HCV treatment with a behavioural intervention that lowers the number of syringes exchanged. Also, we include HCV induced mortality. The latter entails that curing IDUs prolongs their lifetime spent injecting, thereby increasing the total number of syringes lent out. For clarity of the description, we revert to instantaneous and always successful treatment, $v = 0$ and $s = 1$. In order to minimise changes to our formulae, as above, r denotes the risk of the treated IDU from the moment of curing onwards. We define r_b as the number of syringes exchanged by the IDU per month before intervention takes place. μ_c is the additional death rate experienced by chronically HCV infected IDUs.

The additional death rate entails the following redefinitions of the times spent in the chronic infection

state:

$$\begin{aligned} T_{uc} &= \frac{1}{\mu+\mu_c}\frac{(1-d)\theta}{\theta+\mu}\frac{\lambda}{\lambda+\mu}\frac{1}{1-g} \\ T_{ac} &= \frac{1}{\mu+\mu_c}\frac{(1-d)\theta}{\theta+\mu}+\frac{d\theta}{\theta+\mu}T_{uc} \\ T_{cc} &= \frac{1}{\mu+\mu_c} < T_{au}+T_{aa}+T_{ac} \\ &< T_{uu}+T_{ua}+T_{uc}. \end{aligned}$$

For the number of infections prevented to others, b_o, we have to take into account that the index over his complete life-time will now lend out $r(T_{uu}+T_{ua}+T_{uc})$ syringes to others instead of $r_b T_{cc}$ syringes. When not obtaining syringes from the index, individuals will borrow from other IDUs instead, which may also cause them infection with probability $m_a p_a + m_c p_c$. Similarly an individual not infected will lend out $\tilde{r}(T_{uu}+T_{ua}+T_{uc}-(T_{au}+T_{aa}+T_{ac}))$ more syringes by experiencing less HCV induced mortality. We can now calculate the number of infections to others prevented as:

$$\begin{aligned} b_o &= (1-m)(p_c r_b T_{cc} - r(p_a T_{ua}+p_c T_{uc})) - \\ &\quad (r_b T_{cc} - r(T_{uu}+T_{ua}+T_{uc}))(m_a p_a + m_c p_c) \\ \tilde{b_o} &= \tilde{r}(1-m)(p_a T_{aa}+p_c T_{ac}-(p_a T_{ua}+p_c T_{uc})) \\ &\quad -\tilde{r}(T_{au}+T_{aa}+T_{ac}-(T_{uu}+T_{ua}+T_{uc})) \\ &\quad (m_a p_a + m_c p_c), \end{aligned}$$

in the latter with r replaced by $\tilde{r}$ within λ in T_{ij}. All further definitions to obtain the direct and indirect benefits of curing remain as given in sections 3.1 and 3.2. We show numerical results for the influence of HCV induced mortality μ_c in Figure 6, and for risk reduction from treatment onwards in Figure 7.

4. Results

The benefits per IDU treated for HCV, defined here as a lowering in the number of chronic HCV infections, decline with the prevalence of HCV contamination among exchanged syringes m. Considering whom are best treated we found a threshold in m: above the prevalence threshold treating lower risk IDUs, but below it treating higher risk IDUs results in greatest benefits. The threshold occurs since at high prevalence the probability for re-infection dominates the equation for the benefits, while at lower prevalence the potential for preventing infections to others dominates (as shown in Section 3.5).

In our baseline model the threshold is at $m = 50\%$, both when considering only the direct effects of curing, that is in the infection status of the treated IDU and number of infections directly caused by this IDU, and when considering fully the effects in all further infection generations (Figure 3). In our baseline model, the direct effects underestimate the full effects when prevalence among syringes $m < 50\%$, but are an overestimate when this prevalence $> 50\%$.

Adding model complexity influences the threshold value; including that HCV causes mortality, or that acute infection is more infectious than chronic HCV infection, decreases the HCV prevalence above which to treat lowest risk IDUs (Figures 4 and 6). In both cases the term for infections prevented to others is made smaller and thereby less dominant (Sections 3.7 and 3.1). In contrast, with longer duration of treatment, which postpones and renders re-infection less likely, the threshold is shifted upwards (Figure 5, Section 3.6).

Treatment of HCV could be rendered more effective for IDUs by combining it with intervention aimed at lowering their risk behaviour (see Figure 7). Whether this addition to treatment would impact the threshold in m depends on how behaviour is changed. When we lower by a fraction the before treatment syringe sharing rate r_b, the threshold in m above which to treat lowest risk IDUs is moved upwards. In fact, if 100% risk elimination can be achieved, a combination of HCV treatment and risk prevention should always target highest risk individuals (Figure 7A). However, risk reduction might instead be independent of the starting risk of the treated IDU, for example when providing a certain number of clean syringes each month. Such absolute risk reduction would not affect who should be treated (Figure 7B).

5. Discussion and Conclusions

Our aim was to answer, from a public health perspective, as to which IDUs are best treated for HCV infection. We used a simple model in order to gain a most general answer and greatest understanding of the factors determining this question. Our model lacks certain aspects of reality however, which should be considered before implementing targeting of HCV treatment by risk behaviour.

In particular, we did not perform a proper cost effectiveness study of the alternative treatment strategies. In cost-effectiveness studies, benefits and costs that are expected later in time are usually discounted, since they are less certain [12]. We assumed a steady state situation and counted equally infections occurring at any point in time after treatment. However, we did distinguish direct and indirect benefits of intervention, with the indirect benefits mostly accruing later in time. Discounting of future effects could shift the prevalence threshold relating whom to cure somewhat, but in general consideration of only the direct or the full benefits led to the same treatment policy advice.

We focussed on risk behaviour only. In reality there will be other individual factors of relevance for the expected benefits from treatment, such as possible HIV co-infection, age or time since HCV infection. For example, treatment at old age would prevent fewer infections to others, and could be too late to stop liver damage. Including age or time since infection would invalidate the Markov assumption on which our formulae are based, and therefore require a more complicated type of model to study.

In the present model, a case of re-infection after treatment is no different from one of first time infection; it should be treated equally. In reality, occurrence of re-infection might be used as an indication for an IDU's risk behaviour, informing the decision of future treatment.

Our calculations assumed the curing of a single IDU in an infinitely large population, and are therefore not valid when curing a substantial fraction of all infected IDUs. Curing of multiple IDUs would (temporarily) lower HCV prevalence, and the consequent time-dependence would render analytic derivation such as presented here much more complicated. By continually curing a constant fraction of infected IDUs, a new equilibrium would eventually be reached. To determine who are best cured in this situation, our method is adapted by simply considering the new stable proportion of syringes m that would then carry infection.

The benefits from curing specific numbers of IDUs over specific time-windows have been studied numerically, including for situations with changing prevalence over time [4, 5, 6, 7, 8, 9, 10]. With our method, however, we could gain enhanced understanding of how to optimize the HCV treatment benefits, and draw more generalized conclusions. In particular, we could study separately the impact of behavioural and prevalence parameters. We could distinguish parameter domains where HCV treatment benefits are increasing with risk behaviour of the treated IDU from circumstances under which these benefits are decreasing with risk.

Based on our model results, we recommend that HCV treatment policy should be informed by prevalence of HCV contamination among exchanged syringes, m, within an IDU population. This prevalence among syringes might for example be measured from syringe exchange facilities [13]. For the present analysis however, we assumed proportionate mixing. When IDUs do not borrow at random, they do not all experience the same probability to lend from or to someone HCV infected, i.e. m could be related to risk level. Then also, prevalence among syringes would not equal m.

Since those who share syringes most often are most likely to be infected, syringes from infected IDUs are over-represented among the population of exchanged syringes, i.e. prevalence among syringes will be higher than prevalence among IDUs. In future work we plan to explore the relationship between the two types of prevalence. In order to better inform treatment policy, we will also make use of a numerical method for obtaining the benefits B, which allows for more complicated model assumptions, including separate mixing and partial immunity.

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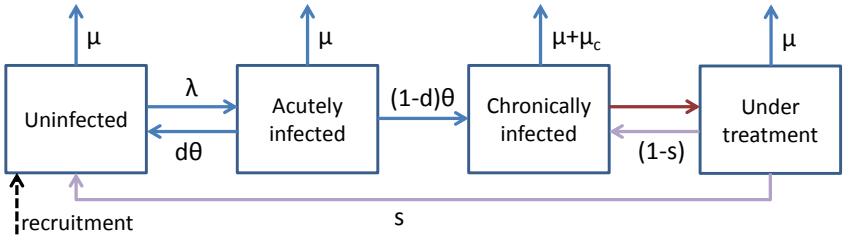
Figure 1: A model of Hepatitis C Virus treatment for Injecting Drug Users



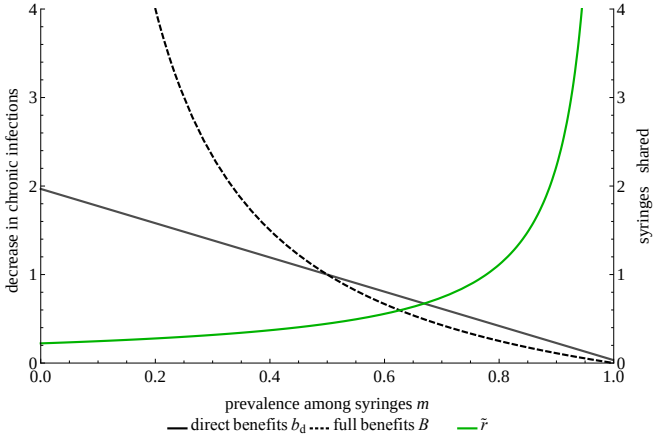
The blue arrows indicate per month probabilities to transition between states. The dark red arrow indicates the act of starting treatment. The light purple arrows indicate the state transition probabilities at the end of treatment, which lasts v months.

Table 1: Parameters and their values as used for the numerical results

Parameter	Baseline value (alternative*)	Description
θ	0.33 per month	Loss rate of HCV acute status
d	0.26	Probability of clearing HCV
p^C	0.05 per syringe	Infectiousness chronic HCV
p^A	0.05 (0.5*) per syringe	Infectiousness acute HCV
μ	0.0083 per month	Death and stop injecting rate
μ^c	0 (0.002*) per month	Additional HCV induced mortality
v	0 (12*) months	Treatment duration
s	1	Treatment success probability

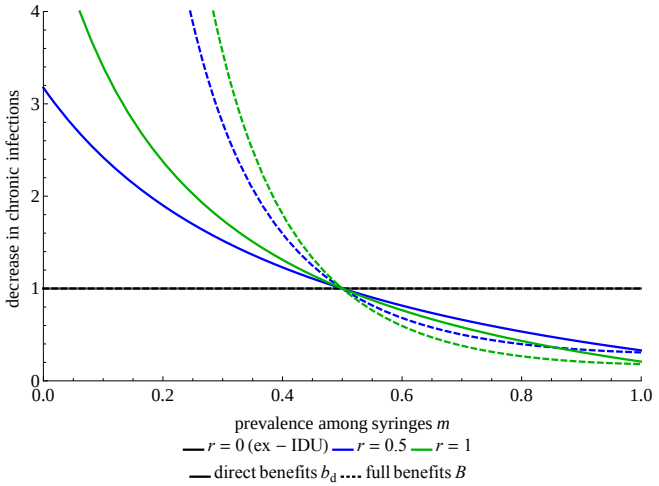
*Alternative values to show parameter effects, Figures 4, 6 and 5 respectively.

Figure 2: Benefits of curing one IDU in a homogeneous population



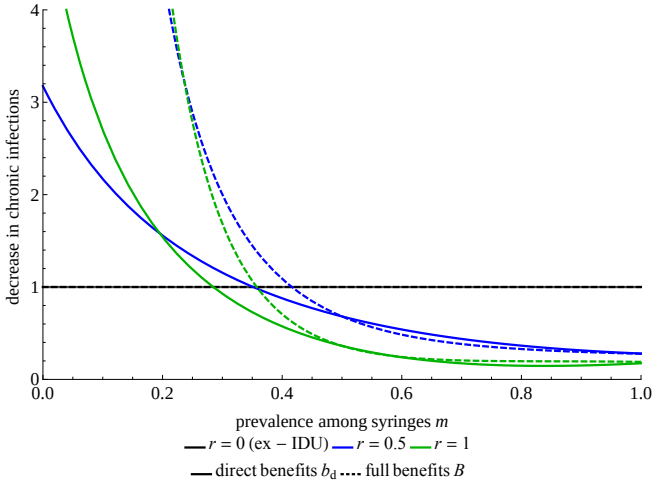
We assume a homogeneous population in which all IDUs, including the treated index, share $\tilde{r}$ syringes per month, resulting in equilibrium HCV prevalence m. Solid black line: Direct benefits b_d of curing one IDU. This includes curing the one IDU (minus their probability for chronic re-infection), and the number of IDUs that would have otherwise been chronically infected by this IDU. Dotted black line: Total effects of curing one IDU. This additionally includes that those not infected by the cured IDU do not infect others, who do not infect others, etc., but also the fact that these IDUs may still become chronically infected by sharing with other IDUs. We find that the direct benefits b_d are an underestimate of the full benefits B when $m < 0.5$, but an overestimate when $m > 0.5$.

Figure 3: Benefits of curing one IDU



Solid lines: Direct benefits b_d of curing one IDU who shares r syringes per month. Dotted lines: Total effects of curing one IDU, B, assuming a homogeneous population in which all IDUs apart from the treated index share $\tilde{r}$ syringes per month, resulting in equilibrium HCV prevalence m. We find that the benefits (both direct and full) increase with risk of the index r when $m < 0.5$, but decrease with risk r when $m > 0.5$.

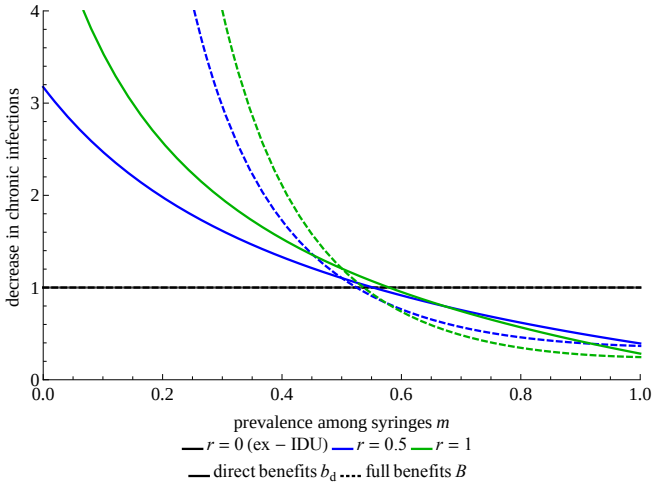
Figure 4: Increased infectiousness during acute infection



The benefits of curing one IDU assuming acutely infected IDUs are ten times as infectious as chronically infected individuals. To calculate the full benefits B we assume a homogeneous population at equilibrium, with all IDUs apart from the index sharing $\tilde{r}$ syringes per month. The difference in infectiousness is especially relevant to the direct benefits b_d. For the cured index we remove chronic infection but thereby allow for a period of more infectious acute infection if re-infection occurs. For infections further in the infection chain, we prevent acute and chronic infection equally, so that the indirect benefits $\tilde{b_d}$ still balance at $m = 0.5$.

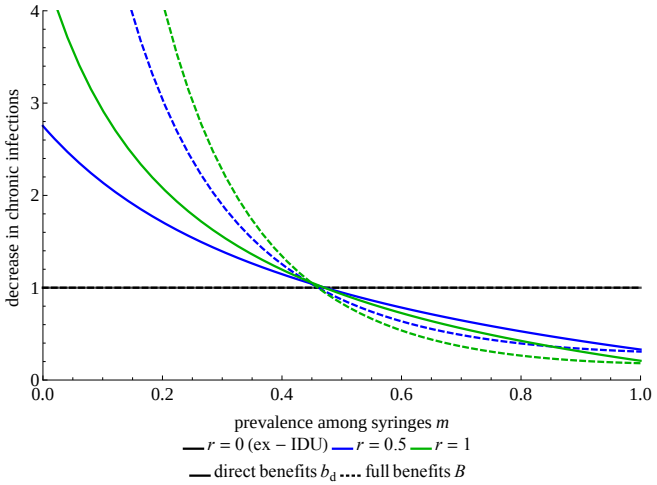
We find that when acute infectiousness > chronic infectiousness, there is an optimum in risk level to target for $m < 0.5$. Therefore we can no longer give a simple threshold value in prevalence among syringes m describing whom to best cure in any not further specified population. However, curing lower risk IDUs will be most beneficial from prevalence among syringes m somewhat below 50% and onwards.

Figure 5: Longer treatment duration



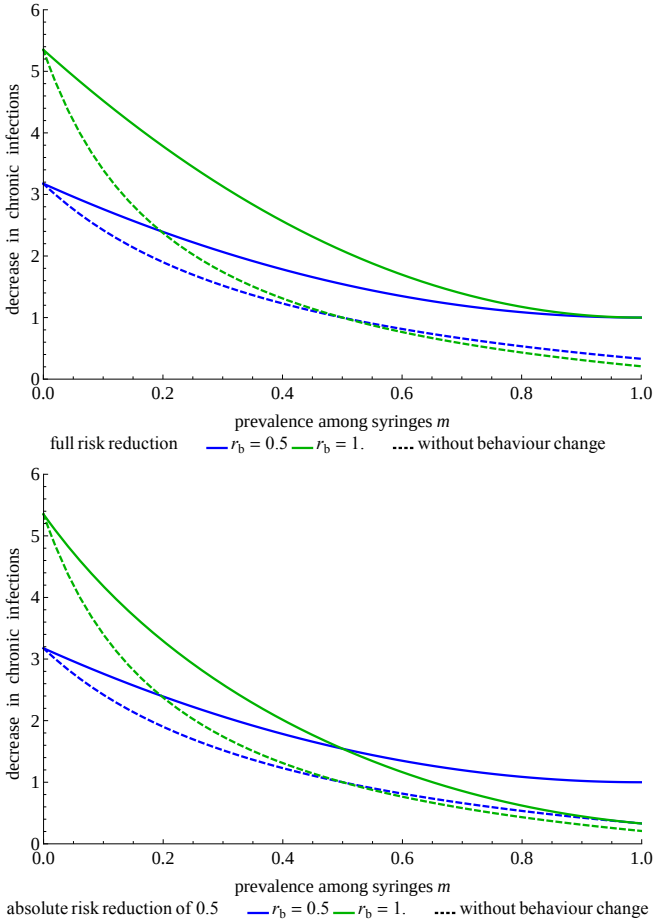
The benefits of curing one IDU assuming treatment duration $v = 12$ months. During this time re-infection cannot take place nor does the treated IDU spread infection. To calculate the full benefits B we assume a homogeneous population at equilibrium, with all IDUs apart from the index sharing $\tilde{r}$ syringes per month. For the indirect benefits $\tilde{b_d}$ treatment duration is irrelevant, therefore the full benefits B are much less affected than the direct effects b_d. We find an optimum in risk level to target when $m > 0.5$, and can no longer give a simple threshold value describing whom to best cure in any not further specified population. However, curing lower risk IDUs will be most beneficial from prevalence among syringes m somewhat above 50% and onwards.

Figure 6: Additional HCV induced mortality



The benefits of curing one IDU when the rate of mortality for chronically HCV infected IDUs is increased by $\mu_c = 0.002$ per month. To calculate the full benefits B we assume a homogeneous population at equilibrium, with all IDUs apart from the index sharing $\tilde{r}$ syringes per month. When HCV causes mortality, the expected time an individual remains infectious is decreased. Fewer infections to others would have been caused, and this renders curing less beneficial. There is an optimum in risk level to target for $m < 0.5$, therefore we can no longer give a simple threshold value in prevalence among syringes m describing whom to best cure in any not further specified population. However, curing lower risk IDUs will be most beneficial from prevalence among syringes m somewhat below 50% and onwards.

Figure 7: Benefits of curing combined with behavioural change



The direct benefits b_d when curing and changing behaviour of one IDU, who before treatment shares r_b syringes per month. For comparison, dotted lines show the benefits without behaviour change. Top) From the moment of curing, all further syringe sharing is prevented, i.e. $r = 0$. Bottom) From curing, the rate of both borrowing and lending by the cured IDU is lowered by 0.5 syringes per month, i.e. we lower pre-treatment risk $r_b = 0.5$ to post-treatment risk $r = 0$, and $r_b = 1$ to $r = 0.5$.

CHAPTER 7

Hepatitis C Virus treatment as prevention among injecting drug users: Who should we cure first?

Hepatitis C Virus treatment as prevention among injecting drug users: who should we cure first?

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Abstract
Background: By treating Injecting Drug Users (IDU) for chronic HCV-infection, we may prevent new infections to other IDU. Treating individuals who often share their injecting equipment is most likely to prevent new infections. However, these IDU are also more likely to become re-infected when compared to IDU with lower risk behaviour. We therefore studied to whom treatment is best targeted.
Methods: We modelled the expected benefits per curing of one chronically HCV-infected IDU. These benefits were defined to include in a single measure both curing and staying uninfected of the treated IDU, as well as prevention of infections to others (i.e. these benefits quantify the expected decrease in chronic infections). We explored the impact of risk behaviour of the cured IDU on these benefits, while varying HCV-prevalence. We also investigated sensitivity to model assumptions, and the impact of HCV-treatment combined with risk-reduction interventions.
Results: We found a threshold in HCV-prevalence above which treating low-risk-IDU, but below which treating high-risk-IDU was most beneficial. This threshold is at approximately half of all exchanged syringes being HCV-contaminated. The corresponding threshold of HCV-RNA-prevalence among IDU is somewhat lower, depending on the distribution of risk-behaviour within the IDU population. The threshold was marginally sensitive to changes in disease and treatment variables. A combination of HCV treatment and risk-reduction was best directed at high-risk-IDU even in a high-prevalence setting.
Conclusion: Where HCV-prevalence is above a threshold of around 50%, we recommend to preferentially treat low-risk-IDU, or to combine treatment with risk-reducing interventions. At lower prevalence however, it would be most effective to treat high-risk-IDU first.
Keywords: HCV prevention; mathematical modelling; risk heterogeneity; injecting drug use; HCV

Introduction

Blood-borne infections are spread among injecting drug users (IDU) by their sharing of contaminated injecting equipment. Especially transmission of Hepatitis C Virus (HCV) via this route is likely: 50% to 90% prevalence within IDU populations is common [1]. Infected individuals can be cured by use of antiviral treatment, thereby preventing the severe liver disease that may result from long term HCV infection [2]. However, treatment uptake among IDU is still relatively low [3]. Physicians may be reluctant to prescribe treatment to IDU as they fear non-adherence and psychiatric side-effects, but also because of a presumed high-risk of re-infection [4].

Much attention has recently been given to the concept of treatment as prevention for HIV [5]. Since treatment of HIV by lowering viral load not only limits health consequences for those infected but also lowers their likelihood of infecting others [6], high treatment uptake has been postulated to allow for elimination of this virus [7, 8]. For HCV the same concept applies, since those cured of HCV will no longer spread the virus to others [9]. This has important consequences for the benefits expected from treating IDU. Modelling work has shown that under a wide range of population settings and incorporating failure rates, partially due to these indirect effects of reduced transmission, HCV treatment of IDU will be cost-effective [10-14].

New treatment options with fewer side-effects and high success rate are becoming available [15]. This development has even led to discussion of the possibility for elimination of HCV, although this goal is not expected to be reached on the short term [16, 17]. In most settings, it will not be possible to offer treatment to all infected IDU at once, e.g. due to constraints in budgets or a suboptimal infrastructure or care-system for IDU [18]. At this time, the improved treatment options are highly expensive. This renders it important to consider how to optimise the population level benefits from treatment.

Targeting treatment according to risk level may enhance the treatment as prevention strategy. Here we examined to whom treatment should be directed first. The likelihood of preventing new infections is highest when curing individuals who often share their injecting equipment, i.e. high-risk IDU. However, this positive aspect of targeting high-risk IDU is offset by their higher probability of becoming re-infected with HCV, which limits the benefits of their treatment both for themselves and for the population.

We introduce a summary measure for the benefits at population level of treating one infected IDU. This measure combines the probability for the treated IDU to become and stay uninfected with the expected number of infections prevented to other IDU. The measure takes into account the total duration of the prevented chronic infections, but not explicitly disease burden. We calculated these benefits per treated individual using a dynamic transmission model, which allowed us to quantify the impact of treatment on HCV incidence, as dependent on the risk-behaviour of the treated IDU.

Whether it is most beneficial to target high- or rather low-risk individuals depends on the prevalence of HCV among circulating syringes. This prevalence among syringes follows from the HCV-RNA prevalence among IDU, depending on the distribution of risk behaviour within the IDU population. The prevalence amongst syringes might be measurable at syringe exchange

facilities, and would provide valuable information on the circulation of the virus in the IDU population [34]. We explored the relationship between prevalence amongst syringes with the prevalence amongst IDU, in order to allow treatment policy to also be fully informed by the latter.

As the evidence base is not equally well established for all factors determining transmission of HCV and disease progression, we explored sensitivity of our results to some of those factors. We also considered the expected changes, i.e. a shorter duration and greater success rate, of HCV treatment.

Methods

We considered a mathematical model for a population of IDU, in which sharing of injecting equipment takes place. During sharing HCV infection can be transmitted, leading to acute infection. From acute infection, an individual either clears infection or develops chronic infection (see Fig. 1). Recovered individuals may have a certain level of protective immunity that lowers their risk of a subsequent infection. In the model, HCV will establish itself at endemic steady state (a stable prevalence that is eventually reached in the population, depending on the sharing rates of the IDU).

We considered the situation that, in this otherwise unchanged population, one IDU is treated. We quantified the decrease in the number of chronic infections due to the treatment of this one IDU. This number we defined as the benefits *B*. We focussed on chronic infections only since cleared acute infection does not cause liver disease. We studied how these benefits *B* depend on the risk

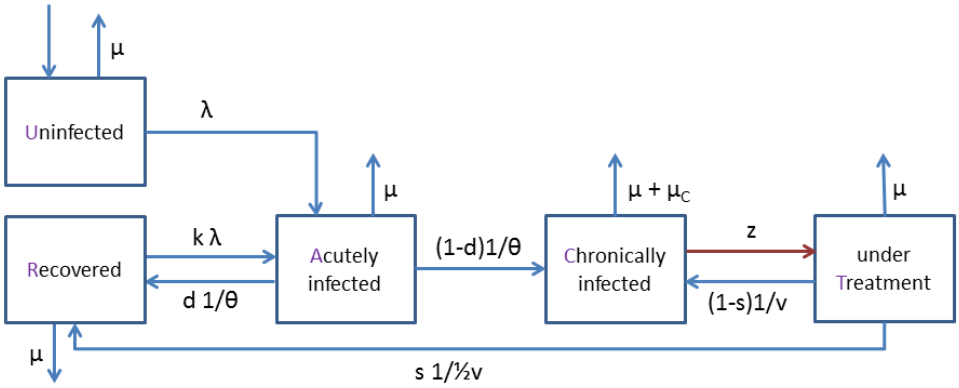

Figure 1. A model of HCV spread among IDU. Individuals are infected with a rate λ, which depends on *r,* the individuals risk in syringes borrowed per month, p_a and p_c, the probabilities to become infected per use of a syringe carrying acute or chronic infection respectively, and m_a and m_c, the probabilities that a borrowed syringe carries acute or chronic infection respectively ($m_a + m_c = m$, prevalence of infection among syringes). For those previously infected the probability for infection is lowered by a factor *k*. Acute infection status is lost with rate 1/θ, at which point infection may be cleared with probability *d*. With complementary probability 1-*d* infection becomes chronic. Ceasing of injecting or mortality occurs with rate μ, HCV-induced mortality with rate μ_C. Treatment lasts a number of months *v*, and with probability *s* treatment is successful in leading to a sustained virological response.

level of the treated IDU.

Our method is fully explained within the Appendix. Below we first briefly explain the main principles of the method, and then we describe the parameter values used in the model

Calculation of the benefits

The benefits *B* of treating of one chronically HCV infected IDU can be calculated as the sum of two parts [19]. The first part is the probability for the treated IDU (the index) to become and remain uninfected. The second part consists of the number of chronic infections prevented to other IDU accumulated over the entire further transmission chain.

Both re-infection of the index and prevention of infections to others will depend on the risk behaviour of this treated IDU. Each injection with a syringe previously used by an infected IDU may cause re-infection, therefore, the more syringes the index borrows, the more likely re-infection becomes. We denote by *r* the per month number of syringes an individual borrows, and refer to this quantity as risk level. We assume that the rate of borrowing syringes equals the rate of lending out used syringes to other IDU. The more syringes are lent out by an infectious IDU, the more infections in other IDU he/she would cause, and the more infections can be prevented by treating that IDU.

After being cured the probability of re-infection will depend on the probability per sharing act that sharing occurs with someone who is still infected; we denote this probability by *m*. The larger *m*, the more likely the index is to borrow from someone infected, and the more likely it is that re-infection of the cured IDU occurs.

For already infected IDU infection cannot be prevented. Therefore, the expected number of infections prevented to others will increase with 1-*m*, which represents the probability that someone borrowing from the index IDU is not already infected. The computation also includes infections prevented further down the transmission chain; those not infected by the cured index will not infect others who will in turn not spread infection etc., although these IDU may become infected by others instead.

In our modelling approach we also take into account such factors as natural clearance and the time spent injecting, see Figure 1. For a full analytic derivation of the measure of benefits *B* we refer to [19]. For the present investigation, we made use of a transmission dynamic model, which allowed us to compute numerical results under more realistic assumptions. This required fully specifying the risk structure of the population. As in earlier work we defined a model population subdivided into two risk sub-groups [20]. The model was run until HCV prevalence was at a constant level, i.e. when equilibrium conditions were reached. Then we perturbed the equilibrium by introducing a very small fraction of treated individuals. We kept track of the change in incidence of new chronic infections per cured individual (see the Appendix).

The probability of sharing with an infected IDU, *m*, can be described as prevalence of HCV contaminated syringes circulating among IDU. We explored how this prevalence among syringes *m* is related to prevalence among individuals, *w*, using also the dynamic population model at equilibrium. All results were obtained using Mathematica version 7.0.

Model parameters

Information is lacking on several factors determining transmission of

HCV and disease progression, especially in IDU. Therefore we defined a baseline model based on best available evidence, but also investigated the effects of several changed parameter values, as shown in Table 1.

Table 1: Parameters and their values as used for the numerical results

Description	Parameter	Baseline value	alternative*
Average duration of acute HCV status	θ	3 months	
Probability of clearing HCV	d	0.26	
Infectiousness chronic HCV	p_c	0.05 per syringe	
Infectiousness acute HCV	p_a	0.05 per syringe	0.5 per syringe
Death and stop injecting rate	μ	0.0083 per month	
Additional HCV induced death rate	μ_C	0.002 per month	0 per month
Average duration of successful treatment	v	8 months	2 months
Average duration of failed treatment	$½\ v$	4 months	1 months
Treatment success probability	s	0.54	0.9
Partial immunity factor	k	0.8	1
Fraction of IDU engaging in high-risk	f	0.42	Full range, 0-1
High divided by low syringe sharing rate	h	7.3	1, 2, 4, 16
Preference to share with same risk IDU	q	0	0.7

*Values used for sensitivity analyses, see Table 2 and Fig. 3 and A1 respectively.

We assumed an acute HCV infection phase lasting an average of 3 months [21], at the end of which 26% of infections were cleared naturally [22]. For HCV-naïve IDU, we assumed a 5% probability of acquiring infection per use of a contaminated syringe [23, 24]. Those who spontaneously or on treatment clear HCV might attain some level of immunity, making re-infection with the primary genotype less likely, but debate on the strength of such immunity is on-going [25, 26, 27]. For our baseline model we assumed a 20% lowered probability of re-infection. We also assumed infectiousness to be constant over the course of infection. However, individuals might actually be more infectious during the acute phase compared to during chronic HCV infection [28, 29], effects of which we investigated as an alternative scenario.

The rate of leaving the IDU population (either by ceasing injecting or by death) was set at 0.0083 per month, corresponding to an average injecting-career-length of 10 years [30]. Since sequelae of HCV infection mostly occur after a period of up to 20 years, most HCV-induced mortality likely occurs in individuals who ceased injecting [31, 27]. In our baseline model we included a HCV-induced mortality rate of 0.002 per month.

Currently, duration of standard treatment with peginterferon and ribavirin is 24 (genotypes 2 and 3) or 48 weeks (genotypes 1 and 4) [15]. In a recent review, among IDU who were prescribed peginterferon plus ribavirin, the median rate of Sustained Virological Response (SVR) was found to be 54%, although values varied widely across studies [3]. As viral load is usually reduced shortly after starting treatment, we assumed that individuals with an SVR are not infectious during treatment [4]. However, a substantial fraction of those starting treatment do not complete treatment [15] and treatment may fail to lower viral load [4]. We

therefore assumed that treatment duration is only half as long for those not reaching SVR.

Future treatment regimens are expected to be shorter and more successful, with over 90% SVR rates reported among the general population [15]. We examined the impact of these changes on the treatment benefits as an alternative scenario.

Individuals were assumed to share injecting equipment with a constant frequency over their time injecting, this risk behaviour determined the model HCV prevalence. We assumed equal rates of borrowing and lending out injecting equipment by the individuals, since receptive and distributive sharing are often part of the same injecting episode, and correlation between the self-reporting of these two risk-behaviours is generally high [32].

Very little is known about the distribution of risk behaviour within IDU populations. We analysed the impact of treatment in a population consisting of two risk sub-groups. Based on data from the Amsterdam Cohort Studies among IDU, we assumed 42% of IDU engaged in high-risk, these sharing syringes 7.3 times as often as the remaining low-risk IDU [20]. We investigated the effects of varying these values, and also considered that syringe exchange might occur preferentially between IDU with similar risk behaviour.

Finally, we considered that treatment of HCV could cause behaviour change, or that it could be combined with behaviour changing harm-reduction interventions (e.g. opiate substitution therapy and needle exchange programmes) [33].

Results

A threshold for the optimal treatment strategy

Figure 2 shows the benefits per curing of one low- or one high-risk IDU, depending on the prevalence of HCV. We observe that the two curves intersect, i.e. at around 35% there is a threshold in the HCV-RNA prevalence among IDU; below this threshold treating high-risk IDU is more effective in reducing the number of chronic infections, above the threshold treating low-risk IDU is more beneficial.

This threshold phenomenon can be explained intuitively as follows. If prevalence is high the probability of preventing infections to others is low, as most of those borrowing syringes are already infected. At the same time, the probability of re-infection is high, and this makes treatment of those least likely to be re-infected most beneficial. If prevalence is low, re-infection risk is not that large. In this circumstance it is most beneficial to cure individuals who lend out many syringes, since they would have infected many other IDU.

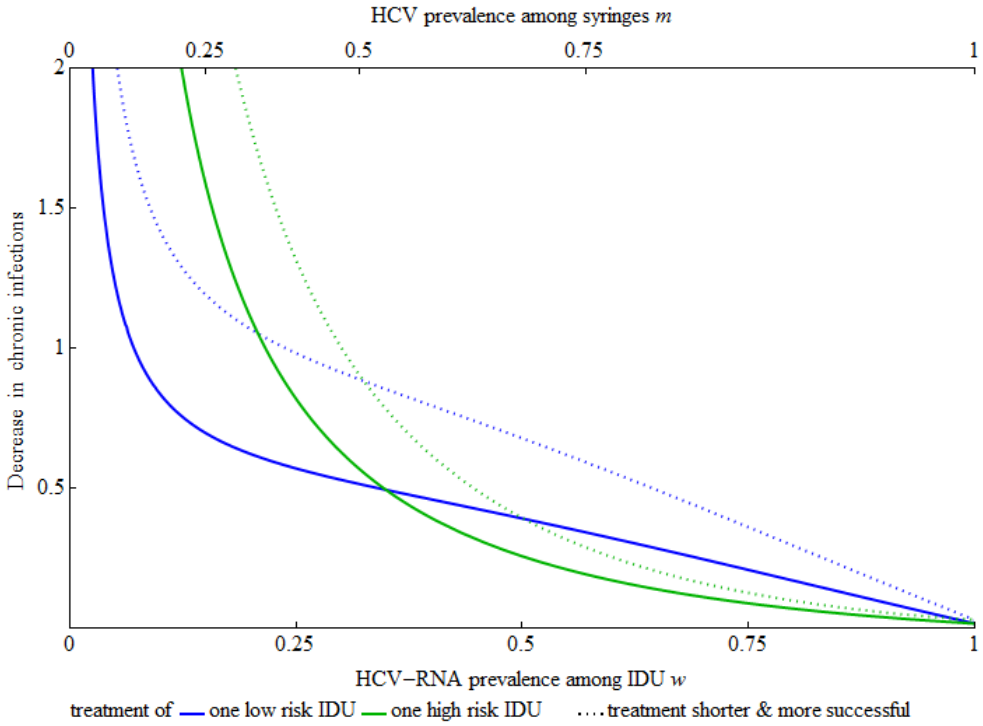

Figure 2. Benefits of curing one IDU in a two-risk-group population. We cure one low or one high risk IDU. The benefits are in terms of a decrease in the number of chronic cases that would have otherwise occurred. The bottom x-axis indicates HCV-RNA prevalence among IDU, for comparison, the top x-axis indicates corresponding HCV prevalence among syringes, *m*. Dotted lines: The benefits when treatment duration has shortened from 8 to 2 months, and the success rate has increased from 0.54 to 0.90.

Prevalence among IDU related to prevalence among syringes

From the perspective of individuals, the prevalence among syringes *m* determines the likelihood of re-infection and of spreading disease to others. We therefore find that this value best informs treatment policy, rather than the corresponding HCV-RNA prevalence among individuals.

Those who most frequently share syringes are most likely to become infected. Reversing this statement, those who are infected are the ones who most often shared syringes, i.e. syringes from infected IDU are overrepresented among the syringes exchanged within the population. This entails that prevalence among syringes *m* is always higher than HCV-RNA prevalence among IDU *w* (see Figure 3). Heterogeneity in risk behaviour in the IDU population determines the relationship between *m* and *w*: the larger the variability in risk behaviour between individuals, the larger the difference between *m* and *w*.

In our baseline scenario the threshold value above which to treat low-risk IDU, at *w*=35%, corresponds to a threshold among syringes *m* at 53%. The threshold remains at *m*=53% when we change the relative sharing rate of high- compared to low-risk IDU, but the corresponding threshold among IDU will be lowest with greatest risk

difference (see Figure 3A). For example, when high-risk IDU share 16 times as often as low-risk IDU (rather than the 7.3 times at baseline) then low-risk IDU should be treated preferentially from 28% HCV-RNA-prevalence among IDU. Especially a relatively small high-risk sub-group could strongly impact the prevalence among syringes without much influencing the prevalence among IDU (Figure 3B).

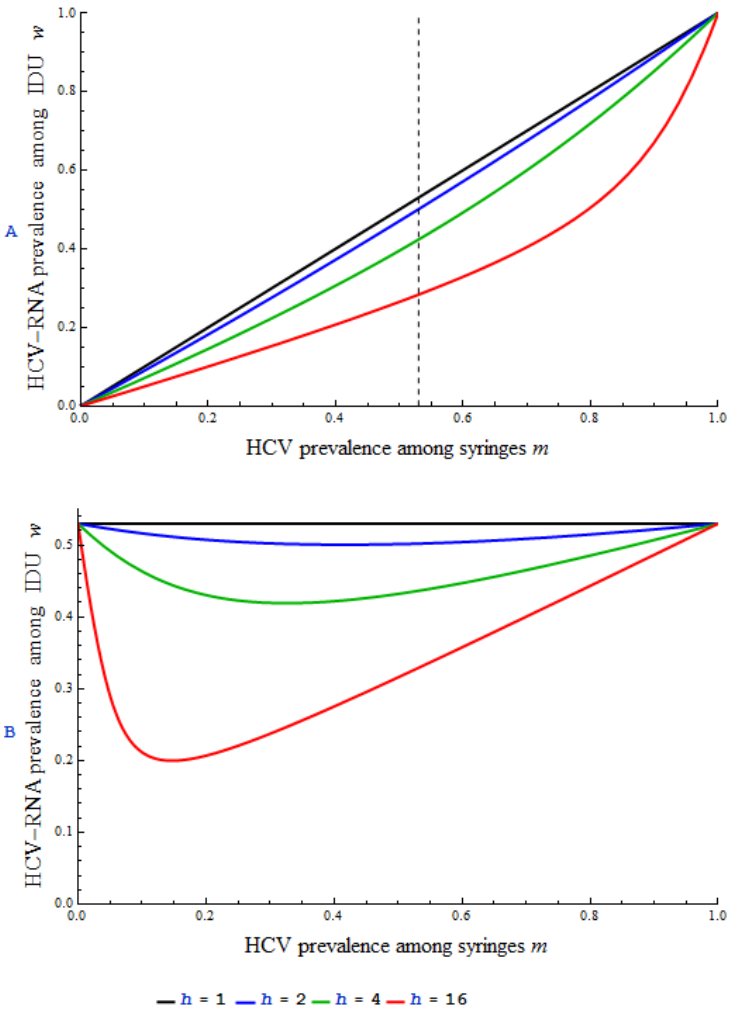

Figure 3. The relationship between HCV-RNA prevalence among individuals *w* and viral prevalence among syringes *m*. A fraction of IDU *f* engages in high-risk. High-risk IDU both lend out and borrow syringes at a rate that is *h* times that of low-risk IDU. (A) The fraction engaging in high risk *f*=0.42. The boundary in prevalence among syringes is at 53%, the corresponding prevalence threshold among IDU can be found along the dashed line. (B) Prevalence among syringes is set at *m*=53%, at the threshold value. The fraction *f* of IDU which engages in high-risk is varied.

Shifting the threshold (sensitivity analysis)

It is expected that future treatment regimens will be shorter with higher SVR rates [15] (dotted lines Figure 2). As we assumed that during treatment re-infection does not take place, shortening treatment duration makes re-infection more likely. This resulted in a slightly lowered threshold above which to preferentially treat low-risk IDU. Increasing the treatment success rate substantially increased the expected benefits, but had minimal effects on the threshold value. In fact, we showed previously that when treatment is instantaneous (or of very short duration), the success rate has no influence on whether high- or low-risk IDU are best treated [19].

From sensitivity analyses we conclude that changing our assumptions on partial immunity against re-infection, HCV-induced mortality, or infectiousness during the acute infection-stage, has minimal impact on our results; in all scenarios the threshold of HCV prevalence among syringes above which to treat low-risk IDU remained near 50% (see Table 2).

Table 2: Sensitivity analysis

Scenario:	Threshold* in prevalence among:	
	syringes *m*	IDU *w*
Baseline	53%	35%
Treatment duration shortened: *v=2*	51%	33%
Treatment more successful: *s=0.9*	52%	34%
No partial immunity: k=1	51%	33%
Acute infectiousness raised compared to chronic infectiousness: p_a=10 p_c	43%	27%
No HCV induced mortality: μ_C=0	56%	37%
70% of syringe sharing preferentially with same risk IDU: q =0.7	-**	22%
Reducing risk of the treated IDU by 20%	57%	38%
Reducing risk of the treated IDU by 50%	64%	45%
Reducing risk of the treated IDU by 100%	100%	100%

*Below the threshold curing high-risk, above it curing low-risk IDU is most beneficial.

** When sharing occurs preferentially between same-risk IDU, prevalence among syringes will be higher for high-risk compared to for low-risk IDU.

Unless stated otherwise, parameters are at their baseline values, see Table 1. Note that only the threshold in prevalence among IDU depends on the distribution of risk within the population.

If sharing occurs mostly between IDU of similar risk (i.e. assortative mixing) rather than at random, the probability to share with an infected IDU, *m*, becomes dependent on risk level. This results in a somewhat lowered threshold above which preferentially low-risk IDU should be treated (see also Appendix Figure A1).

Combining HCV treatment with behavioural intervention

Treatment of HCV could be rendered more effective when combined with intervention aimed at lowering risk-behaviour (last three lines Table 2,

Appendix Figure A2). If we succeed in our prevention efforts and HCV-treated IDU will never again share syringes, re-infection will not occur. In this (unfortunately unrealistic) scenario, high-risk individuals should always be targeted first, since this prevents most infections to others. With less than full risk-reduction, the threshold above which low-risk IDU should be targeted is shifted to higher prevalence levels.

Discussion and conclusions

Our main finding is that who are best approached for HCV treatment is determined by HCV prevalence in the population; when more than half of all exchanged syringes are HCV contaminated, we recommend treating low-risk IDU first, but below this threshold treating high-risk IDU led to greatest benefits. We showed that this threshold, at approximately 50% prevalence among syringes, is not sensitive to variations in transmission and progression risk, or on the success rate or duration of treatment. Furthermore, the threshold expressed in contamination among syringes (as opposed to when it is expressed in prevalence among IDU) is not influenced by the distribution of risk-behaviour within the population of IDU.

Kaplan and Heimer formulated a circulation theory of needle exchange [34]. This allowed them to draw conclusions on HIV prevalence reduction among IDU from information on the prevalence among syringes, which were brought to syringe exchange facilities. Here we suggest that this kind of information might also inform strategies for targeting HCV treatment.

We examined the relationship between prevalence among syringes and the prevalence among IDU, so that policy may also be informed by the latter, especially when some information on the risk distribution is available (see Figure 3). HCV prevalence among syringes will generally be greater than prevalence among IDU, therefore where the latter exceeds 50%, so will the former.

We considered and quantified benefits of HCV treatment by isolating the effect of treating one single individual. The great advantage of this approach is that it allowed us to study the influence of risk-behaviour on the benefits directly, as separate from the impact of treatment on HCV prevalence. This allowed us to identify the circumstances determining the optimal treatment allocation, allowing us to give a more generic answer to the question of who are best treated first. The impact of substantial treatment uptake on HCV prevalence should be kept in mind however; a switch in strategies may become necessary when HCV-RNA prevalence drops below the threshold.

Using a population model where all IDU had equal risk behaviour, Martin et al. found that at 20% or 40% HCV-RNA prevalence active-IDU were best treated, but at 60% prevalence treating ex-IDU was found to be most cost-effective [14]. Based on their population modelling study, Zeiler et al. concluded that HCV treatment should be mostly allocated to those currently not under methadone treatment (i.e. high-risk IDU) [13]. Both studies are in line with our findings.

The sequelae of chronic HCV infection usually only occur decades after infection [31, 27]. In terms of disease burden therefore, treatment relatively early during chronic infection is comparable to preventing the infection altogether. In our approach we assumed timely treatment and therefore treatment and prevention are considered as having similar effects on

disease burden. They contribute equally to the estimated benefits.

We did not formally compute the treatment benefits in terms of a gain in quality adjusted life years or monetary costs. Considering timely treatment, it is expected that such an analysis would lead to similar conclusions with respect to the effectiveness of targeted interventions. However, when treating individuals late in their infection, i.e. after development of substantial liver cirrhosis, curing of an infection has less direct health benefit compared to prevention of an infection. This could change who are best treated.

The support individuals receive to increase treatment adherence may as a positive side-effect lower their risk behaviour in the long-term. This might explain the low rates of re-infection that have been reported in several post-treatment studies among DU [35]. Alternatively, low rates of re-infection could be explained by the fact that so far mostly low-risk IDU have received treatment [4]. Harm reduction interventions, such as opiate substitution treatment and clean needle and syringe provision, may substantially lower the rate of sharing injecting equipment [33]. We found that even when HCV-RNA prevalence among syringes >50%, HCV treatment combined with such risk reduction may be best directed at higher-risk IDU.

It should be kept in mind that models always represent a simplification of reality. We assumed that individuals do not change their risk behaviour spontaneously, although switching between risk-levels likely does occur in reality. Such switching would decrease the difference in the benefits expected from treating different risk-level IDU, but it would not affect whom to best treat [36]. Only if such switching is very common, so that risk always averages out over an individual's injecting career, does targeting of treatment by risk-level become pointless.

We considered only a single generic type of HCV, but we did investigate sensitivity of our results to several of the disease parameters. Our model included only two levels of risk-behaviour. However, our results generalize to best treating the IDU with the low*est* or rather the high*est* risk, when considering a continuum of risk for the treated index [19].

Another important simplification is that aside from their syringe sharing rates we assumed all individuals to be equal. Other factors could also play a role when deciding on the prioritising of treatment allocation. For example, HIV-co-infected or older individuals are likely to have fewer life years to gain from treatment, and since they are expected to die or limit injecting sooner, curing them would prevent fewer infections to others. Therefore, from a public health perspective, it may be most beneficial to prioritise HCV treatment for HIV-uninfected and younger IDU. Also, treating acute infection could enhance the rate of treatment success (although it would pre-empt spontaneous clearance) [3, 37].

Naturally, the projected increase in benefits from targeting treatment depends on the possibility of identifying IDU with different risk-behaviour, and their willingness and opportunity to receive HCV-treatment [38, 36]. High-risk IDU might for example be found in specific venues (shooting galleries), homeless shelters or prisons [39]. Those already participating in harm-reduction interventions however, with already lowered risk behaviour, might be most easily reached. Better compliance with the HCV treatment-regimen among low-risk IDU would also shift the balance in favour of treating them first [38].

In conclusion, targeting HCV treatment by risk-level of IDU could enhance the population level benefits gained, rendering this intervention more efficient. In the past, treatment has been withheld of active IDU, partially due to fears for non-adherence and psychiatric side-effects, but also due to expectations for their likely re-infection [40]. Although re-infections might indeed occur, taking prevention of infections to others into account, treating first high-risk IDU may actually be the optimal strategy, at least where HCV prevalence among syringes is <50%, or where risk-behaviour reduction is at the same time achieved.

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Appendix to: HCV treatment as prevention among IDU: who should we cure first?

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August 13, 2014

1 A population model for HCV among IDU

We determine the benefits of treating one IDU, B, defined as a reduction in the number of chronic HCV infections. For a full explanation and analytical exploration of these benefits we refer to de Vos and Kretzschmar 2017 [19]. Here we make use of a model consisting of differential equations, which describes infection dynamics in a population of IDU. We numerically compute the benefits by considering a small perturbation from the endemic equilibrium by curing an infected IDU. For the principle of this method and a figure representation of the model, see main text.

With this population based method, the prevalence of HCV follows from the population risk level and risk structure. Also, as compared to our previous analytic exploration, the present method allows for several more complicated assumptions, such as partial immunity to re-infection and segregated mixing of the IDU. We additionally explore with this model how, when prevalence has reached an endemic steady state, the HCV-RNA prevalence among IDU w relates to the HCV prevalence among syringes m.

1.1 A differential equations model

The population consists of two risk behaviour subgroups, which are distinguished by their rates of sharing syringes. Low risk IDU borrow and lend out r syringes per month. The equilibrium population size is determined by population inflow Λ, which we take constant in time. A fraction f of these newly injecting individuals are high-risk, these share syringes h times as frequently as low-risk IDU.

We denote the probability that an IDU preferentially borrows from or lends to an IDU with similar risk by q, the remaining fraction $1-q$ of syringe exchanges occurs at random, i.e. we assume proportionate mixing. By z_l and z_h we denote the per month rate of curing low-risk and high-risk IDU, respectively.

We define p_c, the probability of becoming infected when using a syringe contaminated by a chronically infected IDU, and p_a, the same when using a syringe previously used by an acutely infected IDU. For cured IDU (those who naturally cleared or were treated for HCV infection), the probability of becoming infected is lowered by a factor k.

Individuals move out of the acute HCV phase with rate $1/\theta$, where d gives the proportion of these infections being cleared and $1-d$ the proportion of infections leading to chronic HCV. μ is the death or stop injecting rate, μ_c the additional death rate experienced by chronically HCV infected IDU.

With s we denote the probability that treatment is successful in clearing HCV. Immediately upon starting treatment the IDU is no longer infectious, but during treatment the IDU cannot be re-infected. When successful, treatment lasts an average of v months. Unsuccessful treatment lasts half as long, on average $v/2$ months.

Changes in numbers of IDU uninfected U, acutely infected A, being treated successfully T, being treated unsuccessfully F, chronically infected C and recovered R (that is uninfected but partially immune IDU) are described by:

$$
\begin{aligned}
\frac{dU_l}{dt} &= \Lambda(1-f) - r(p_a m_{a,l} + p_c m_{c,l})U_l - \mu U_l \\
\frac{dA_l}{dt} &= r(p_a m_{a,l} + p_c m_{c,l})U_l + rk(p_a m_{a,l} + kp_c m_{c,l})R_l - \frac{1}{\theta}A_l - \mu A_l \\
\frac{dC_l}{dt} &= \frac{1}{\theta}(1-d)A_l - (\mu + \mu_c)U_l - z_l C_l + \frac{2}{v}F_l \\
\frac{dT_l}{dt} &= sz_l C_l - \frac{1}{v}T_l - \mu T_l \\
\frac{dF_l}{dt} &= (1-s)z_l C_l - \frac{2}{v}F_l - \mu F_l \\
\frac{dR_l}{dt} &= \frac{1}{v}T_l + \frac{1}{\theta}dA_l - rk(p_a m_{a,l} + kp_c m_{c,l})R_l - \mu R_l \\
\frac{dU_h}{dt} &= \Lambda f - rh(p_a m_{a,h} + p_c m_{c,h})U_h - \mu U_h \\
\frac{dA_h}{dt} &= rh(p_a m_{a,h} + p_c m_{c,h})U_h + rhk(p_a m_{a,h} + p_c m_{c,h})R_h - \frac{1}{\theta}A_h - \mu A_h \\
\frac{dC_h}{dt} &= \frac{1}{\theta}(1-d)A_h - (\mu + \mu_c)U_h - z_h C_h + \frac{2}{v}F_h \\
\frac{dT_h}{dt} &= sz_l C_h - \frac{1}{v}T_h - \mu T_h \\
\frac{dF_h}{dt} &= (1-s)z_l C_h - \frac{2}{v}F_h - \mu F_h \\
\frac{dR_h}{dt} &= \frac{1}{v}T_h + \frac{1}{\theta}dA_h - rhk(p_a m_{a,h} + p_c m_{c,h})R_h - \mu R_h
\end{aligned}
$$

with

$$
\begin{aligned}
m_{a,l} &= q\frac{A_l}{n_l} + (1-q)\frac{r_l A_l + rhA_h}{r_l n_l + rhn_h} \\
m_{c,l} &= q\frac{C_l}{n_l} + (1-q)\frac{r_l C_l + rhC_h}{r_l n_l + rhn_h} \\
m_{a,h} &= q\frac{A_h}{n_h} + (1-q)\frac{r_l A_l + rhA_h}{r_l n_l + rhn_h} \\
m_{c,h} &= q\frac{C_h}{n_h} + (1-q)\frac{r_l C_l + rhC_h}{r_l n_l + rhn_h} \\
n_l &= U_l + A_l + C_l + T_l + F_l + R_l \\
n_h &= U_h + A_h + C_h + T_h + F_h + R_h
\end{aligned}
$$

The model is represented in Figure 1 of the main text. All numerical results were obtained using Mathematica version 7. Setting $q = 0$, we get $m_{a,l} + m_{c,l} = m_{a,h} + m_{c,h} = m$. We can then relate prevalence among syringes m to prevalence among IDU $w = \frac{A_l+C_l+A_h+C_h}{n_l+n_h}$ (see Figure 3 in the main text).

Using this model we can also compute the full benefits of curing one IDU, B. We do so by comparing the monthly incidence of HCV infection in the steady state without curing, i.e. $z_l = z_h = 0$, and with a small value of those curing rates, i.e. setting $z_l = \epsilon$ or $z_h = \epsilon$. If ϵ is chosen small enough, the impact of curing on prevalence will be negligible. We then compute the impact per one cured individual by dividing the difference in monthly chronic incidence by the monthly number of cured individuals:

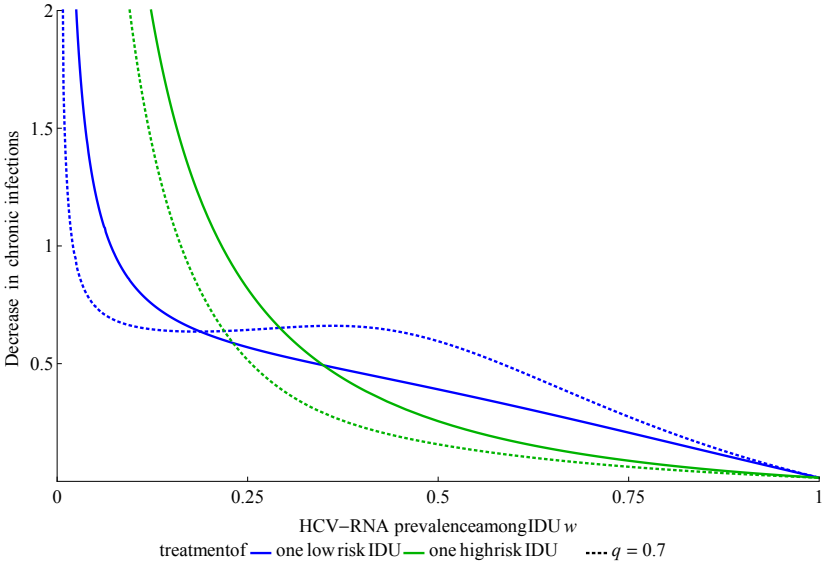
$$\frac{(1/\theta)(A_l + A_h)^0 - (1/\theta)(A_l + A_h)^\epsilon}{z_l C_l + z_h C_h}$$

where superscript 0 denotes equilibrium values without cure and superscript ϵ denotes those values for a treatment rate of ϵ of low or high risk IDU respectively. We add $se^{-\mu v}$ to this result to take into account curing of the treated IDU (including survival of treatment). Note that the possibility for chronic re-infection of this one IDU is taken into account, as it increases the incidence of chronic infections we measure in the population.

By this method, literally, we calculate at a single point in time the total lowering in incidence which is due to the constant rate of curing IDU at all past moments. This logically equals the totalled decline in incidence over all future time points when curing at a single moment; the time that elapses between curing and the effect on incidence is equal in the two situations. The benefit of this method is that we do not need to presume a specific population size, with a certain substantial number of cured IDU. Instead we study the effects of curing one IDU on the number of prevalent cases in an ideal, generalised setting, without curing affecting the prevalence of disease within the IDU population.

Numerically we found B, as calculated by our method here, to agree with B as obtained by our method based on probability calculation, which sums the expected decrease in infected cases over the complete transmission chain from one treated IDU, including the infection status of the treated IDU (see [19]).

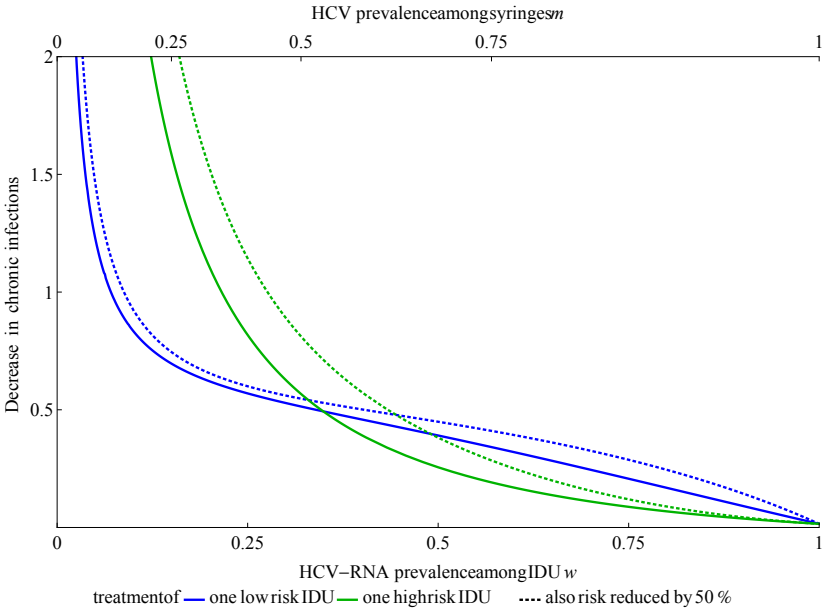
Figure A1: Benefits of curing one IDU as influenced by separate mixing



The benefits B of curing one IDU in a two-risk-group population at equilibrium. Solid lines: the two risk types mix homogeneously, $q = 0$. Dotted lines: $q = 0.7$, that is 70% of sharing events occur preferentially with IDU of similar risk, remaining sharing events occur at random. For remaining parameter values, see Table 1 in the main text.

With segregated mixing, the probability that sharing takes place with an infected individual becomes higher for the high compared to for the low risk IDU ($m_{a,h} > m_{a,l}$ and $m_{c,h} > m_{c,l}$). This decreases the benefit of curing one high risk IDU (their re-infection is made more likely, fewer infections to others are prevented), which lowers the threshold above which to preferentially cure lower risk IDU.

Figure A2: Benefits of curing and decreasing risk of one IDU



The benefits B of curing one IDU in a two-risk-group population at equilibrium. Dotted lines: For the treated IDU, we additionally decrease the syringe sharing rate by half.

CHAPTER 8

Summary in English

Highlights of this thesis

- The simultaneous spread of both HIV and HCV among Injecting Drug users (IDU) is addressed using mathematical modelling
- The importance is shown, when examining effects of interventions, of accounting for:
  - Changes in demography of IDU populations over time
  - Heterogeneity in injecting risk-behaviour among the IDU
- It is shown how policy effects may be enhanced when targeting interventions by level of risk-behaviour

Chapter 1

Harm Reduction denotes policy that aims at reducing the damage that drug users cause to themselves and to society. This policy includes educating drug users and providing them with clean injection equipment or substitution therapy (e.g. methadone), in order to prevent the transmission of blood borne infectious diseases. One infection that affects many Injecting Drug Users (IDU) is the Hepatitis C Virus (HCV), which can cause liver cirrhosis and liver carcinoma. The virus that causes AIDS, HIV, is also spread by shared injecting equipment. Mathematical models give us insight into the expected future spread of such infections among IDU, which aids in improving prevention policy.

Chapter 2

We first developed a deterministic model of the spread of both HIV and HCV among IDU. Both HIV and HCV prevalence are dependent on injecting risk-behaviour; when syringes are shared more often more of the individuals eventually become infected. Since HCV is approximately ten times as infectious through blood to blood contact compared to HIV, HCV is present and much more prevalent within almost all IDU populations. Therefore HCV prevalence has been put forward as a potential measure for the risk for an outbreak of HIV in populations of IDU.

We calculated R_0 for HIV, which is the expected number of new HIV cases that one single HIV infected individual would cause in a fully susceptible population, with R_0 greater than one indicating the potential for an HIV outbreak. We found that for the expected HIV to HCV ratio, it is very important how risk is distributed within a population. For a certain HCV endemic prevalence; the more heterogeneous the rate of sharing, and the more likely individuals are to share with someone of their own risk-level, the greater the potential for spread and expected eventual prevalence of HIV.

To inform the model risk-behaviour we analysed self-reported behavioural data from the Amsterdam Cohort Studies (ACS) on injecting drug users. In particular, we fitted a model with multiple risk groups to answers given to the question "when did you last inject using a borrowed syringe?". Results of the analysis indicated strong heterogeneity in risk-behaviour; our best fit to this data had about one third of the population sharing syringes about seven times as frequently as remaining IDU.

Chapter 3

In a number of countries, including the Netherlands, incidence of HCV and especially that of HIV has strongly declined within the past several decades. It remains unclear, however, in how far this decline can be attributed to the implementation of Harm Reduction policy, since other large changes have occurred at the same time. For example, in recent years fewer new individuals have started injecting drugs in Amsterdam, so that the average age of injectors has strongly increased. For Amsterdam, we attempted to determine how much of the decline in HIV and HCV incidence was due to the services provided to the drug users, and how much due to changes in the population itself.

We created a mathematical model of the spread of HIV and HCV among the IDU in Amsterdam within the past fifty years. This is an individual-based model, each individual has a probability per time-step to become infected or die, and also factors such as age and time since HIV-infection are updated at each monthly time-step.

Parameters such as the age-distribution of new injectors, the probability to discontinue injecting, and the mortality rate (depending on age and current drug use), were based on data from the Amsterdam Cohort Studies (ACS). This is one of the longest on-going drug user studies to date. Gathering of individual information, including HIV and HCV status, started in 1985, only a few years after the first HIV cases occurred among Amsterdam IDU. The number of new individuals entering the model population was based on data of needle-exchange and methadon provision. Data from a collaboration of several cohorts (CASCADE) was used to inform an additional HIV-induced mortality among IDU, dependent on age and time since HIV-infection.

risk-behaviour of the IDU in the model, the extent to which they share their injection equipment, was based on the model fit with the prevalence and incidence data of HIV and HCV from the ACS. A good fit was achieved only when assuming that about one third of the individuals shared their injecting equipment much (ten times) more often compared to the remaining IDU, resulting in their greater likelihood of becoming infected with both viruses. Additionally, to achieve within the model the observed quick initial rise in HIV, we assumed that individuals shared mostly with those of similar risk-behaviour.

It was not necessary to assume changes in risk-behaviour over calendar time for the model to reproduce the strong decline observed in the HIV prevalence and the HIV and HCV incidence. However, the slight decrease in HCV prevalence was obtained only in this way. In conclusion then, with this study we could not show large effects of the Harm Reduction policy in Amsterdam. Although the policy may have impacted IDU risk-behaviour, probably much of the decline in incidence was caused by ageing of the population and the natural progression of the epidemics. In this, it is especially important that those with highest risk-behaviour became infected and died of HIV first.

Chapter 4

Recently, high expectations have arisen for the use of antiretroviral therapy of HIV-infection as a preventive measure. The therapy was developed in order to reduce morbidity of those infected, but by lowering their within blood viral concentration, as a side-effect the therapy lowers their probability of infecting others. The above described individual-based model allowed us to quantify the extent to which therapy in the past has affected the HIV epidemic among the Amsterdam IDU. By adapting the demographics of the modelled population, we could subsequently study for alternative settings the potential impact of different treatment uptake levels on incidence among IDU.

From comparing results of our model for Amsterdam with and without inclusion of

historical HIV treatment uptake, we conclude that HIV therapy in the past has not much affected HIV incidence among IDU in Amsterdam. IDU under treatment were less infectious, but this effect was compensated by the fact that these individuals remained alive longer, during which time they could continue to infect others.

In the past, treatment was usually started only in an advanced disease stage of infection. Starting treatment of IDU in an earlier stage of infection could greatly impact spread of the virus, for which the IDU would need to be tested sufficiently often. For example, with IDU starting therapy on average at one year after becoming infected, we found that incidence over the first thirty years of an HIV epidemic could be approximately halved. However, in order for treatment to have much effect on incidence, it is also very important for the treatment strategy to be implemented within the first few years from the first HIV cases occurring within a population. This applies especially for a population which is declining in size, by a diminished inflow of new IDU.

We also examined effects of the intervention on incidence for populations with different risk structure. Importantly, we noted that simplifying by considering all IDU to be alike in their risk-behaviour, rather than assuming a more realistic level of risk heterogeneity, led to a large overestimation of the expected treatment benefits.

Chapter 5

From the above models we learned that risk-behaviour is likely to be highly variable among IDU, and that this heterogeneity will impact on the effects of Harm Reduction policy. Policies may also be improved by taking this heterogeneity into account; interventions could be directed specifically at IDU of a certain risk-level, thereby rendering such intervention more effective per IDU reached.

We used first a deterministic model of HCV and HIV spread among IDU for studying the effects of targeted intervention. For this analysis we subdivided the model population into two sub-groups, distinguished by their syringe sharing rates. We simulated untargeted intervention, and targeting of intervention to those with greatest, or rather to those with lowest risk-behaviour. We investigated two types of interventions, namely provision of clean syringes to a group of IDU, and isolation or opioid substitution treatment, which was implemented as the ceasing of all risky injecting by individuals.

For a better understanding of how sharing frequency determines the benefits of an intervention, we also developed a calculation of the intervention effects per individual. These benefits firstly include the probability that the intervention prevents the individual under intervention from becoming infected. We also added to the benefits the number of infections expected to be prevented from this IDU to other IDU, by her diminished sharing of injecting equipment.

We found that targeting interventions to specific sub-populations of IDU could indeed make policy much more effective when considered per distributed syringe or per IDU reached. However, who are best targeted depended on the disease and the circumstances under consideration. Perhaps counter-intuitively, sometimes it may be best to target low-risk IDU. High-risk-behaviour individuals, who share injecting equipment frequently, will often be infected by HCV already before they are reached by Harm Reduction services. More HCV-infections may be prevented therefore when focussing on individuals with low-risk-behaviour, of whom a larger proportion are not yet infected.

We found that in general most HIV-infections are prevented when targeting those with highest risk-behaviour. The difference with HCV is due to the less efficient spread of this virus, so that prior to being reached by intervention, usually even the high-risk IDU are not yet infected with HIV.

Chapter 6

HCV may be cured by use of antiretroviral drugs. Due to the side-effects and long treatment-duration of the current standard therapy, as well as the possibility for subsequent re-infection with HCV, few IDU have received this treatment so far. Recently improved albeit much more expensive drugs have become available; these shorten the duration and greatly increase the success rate of treatment.

Curing of HCV will directly prevent adverse health outcomes for the cured individual, but it will also stop the spread of HCV to others. New infections are prevented especially by curing those individuals that would have infected many others, that is those that most often share their injecting equipment. However, for these high-risk IDU re-infection with HCV is also more likely to occur. We therefore investigated who are best treated first, those with higher or rather those with lower risk-behaviour.

We used probability calculation to obtain the population level benefits per treatment of one IDU. Treatment may lead to successful curing of an individual, but this benefit is diminished by the likelihood for re-infection. We added to the benefits the number of infections expected to be prevented to other IDU. These benefits were studied as a function of risk-behaviour, the rate of sharing of syringes, by the treated IDU.

Who are best treated for HCV was found to be determined by the HCV prevalence among exchanged syringes; when more than half of all shared syringes carried HCV-infection, re-infection of high-risk IDU was so likely that treatment of low-risk individuals was most prudent. At prevalence among syringes lower than fifty percent however, first treating people with highest risk-behaviour was most beneficial, since this prevented most infections to others.

Chapter 7

The above problem of the most efficient targeting of HCV treatment was further studied using a deterministic population model. This deterministic model allowed for inclusion of some additional features, such as partial immunity to re-infection for those previously infected.

Using this population model, we could also investigate how the HCV prevalence among shared syringes is related to the HCV prevalence among IDU. We found that the more risk heterogeneous an IDU population is, the more the HCV prevalence among the shared syringes will be higher compared with the viral prevalence among the IDU.

Considering who are best targeted for treatment, we found no great effect of the additional features included in this model. Also the the expected changes in the duration and success rate of the treatment were not found to be of consequence for whom to target. Below approximately fifty percent prevalence among exchanged syringes, treatment of high-risk IDU lowered HCV prevalence most. Conversely, above this prevalence level treatment of low-risk IDU was most beneficial.

We also added a risk-reduction intervention to the HCV treatment. This combination of services was best directed at high-risk IDU up to higher levels of HCV prevalence.

CHAPTER 9

General discussion; Why heterogeneity in risk matters, and how to measure and model it

Heterogeneity in risk-behaviour matters

In the nineteen twenties a first simple model of the spread of infectious disease was put forth by Reed and Frost [71]. This model applied the law of mass action, known from chemistry to describe solutions in dynamic equilibrium, to a population of potential infection hosts, which, like the molecules in the well mixed solution, would meet each other at random. Countless additions to this mathematical model as well as alternative types of modelling have appeared since. One important such addition being that not all potential hosts are alike in their rate of meeting other potential hosts.

The importance of heterogeneity in risk-behaviour was noted in the nineteen eighties in the analysis of models on the sexual spread of HIV [22]. The basic reproductive number R_0 represents the number of new infections expected to be caused by one first infected individual over her entire infectious life-time. When all individuals are equal with respect to their risk-behaviour, R_0 will simply scale with the rate of risk-contacts made by the individuals. In a heterogeneous population, with the individuals still mixing at random, R_0 was found to scale with the average in risk-contacts plus the variance divided by the average in risk-contacts. That is, heterogeneity increases R_0, making it more likely for an outbreak to occur. At the same time, heterogeneity was found in most cases to lower the eventual prevalence reached by HIV.

By sharing of contaminated injecting equipment, blood-borne infections are spread among Injecting Drug Users (IDU). A first model study which incorporated heterogeneity in risk-behaviour among IDU was that by Greenhalgh in 1996 [17]. In their mathematical model, the population was subdivided into a fixed number of risk-sub-groups, and all injecting was assumed to take place at so called shooting galleries. Within shooting galleries needles were shared at random, but the IDU in the separate sub-groups differed in their rate of injecting and in their likelihood of visiting specific shooting galleries. The authors proved that for most parameter ranges the HIV prevalence would eventually approach a stable positive value. They also showed how the R_0 for HIV would increase with risk heterogeneity.

Commonly more than half of all individuals in an IDU population carry chronic HCV-infection [44]. HIV prevalence is more variable, from virtually absent in some to over 40% among IDU in several countries [40]. The different combinations of HIV with HCV prevalence could be explained by different distributions in syringe sharing frequency, with a higher HIV to HCV proportion being expected within more risk heterogeneous populations (see chapter two of this thesis). HIV spread may be much enhanced by a small sub-group of IDU who share injecting equipment frequently. HCV spread will be much less impacted by these high-risk IDU; as HCV compared to HIV is much more infectious by blood to blood contact, this virus spreads readily even among lower risk IDU.

The fact that IDU are not all alike in their equipment sharing rates may also explain epidemic patterns over time (see chapter three of this thesis). One explanation for the strong decline in HIV incidence and prevalence observed among Amsterdam IDU is that those with highest risk died of HIV first, leaving a population of lower risk IDU. Ignoring heterogeneity in risk can lead to overly optimistic expectations for the effects of interventions (for example for treatment as prevention, see chapter four of this thesis). On the other hand, recognition of risk differences might represent an opportunity; interventions may be more effective when directing them at IDU of specific risk-level (see chapters five to seven of this thesis).

As stated in the introduction, the art of modelling lies in including only those aspects of reality that matter for a specific research question, the problem under investigation. To properly judge whether a certain factor is of importance, outcomes of models with

and without this factor of interest should be compared. We found that heterogeneity in injecting equipment sharing rates was indeed a very important factor to consider for the spread of HIV and HCV within populations of IDU. Yet many modelling studies still assume that (apart from intervention effects) all IDU are equal in this risk-behaviour [23, 8, 42]. One reason to omit variability in risk is the lack of reliable data to inform model parameters [25]. Here I discuss diverse ways that equipment-sharing risk-behaviour among IDU has been investigated. I also discuss how others have modelled the risk structure among IDU, and new methods that are being developed to study their risk-behaviour.

The various ways of measuring and modelling drug injecting risk-behaviour

Indications for risk heterogeneity from self-reports

Much can be learned from talking to the people who inject drugs themselves; in depth interviews elucidate their reasons for continued risk taking despite availability of interventions. Withdrawal symptoms and craving were cited as compelling reasons to share, but for poor IDU, sharing also resulted from the need to pool money for drugs [47]. Willingness to share was found to be associated with levels of perceived risk, which in turn was strongly correlated with social distance; most IDU were more willing to share with sexual partners and good friends than with strangers [56]. The social distance beyond which no sharing occurred, however, differed between IDU.

Many studies show that self-reported risk is associated with other variables, for example gender, age and ethnicity, type of drugs used, incarceration or homelessness [55, 11, 28, 72, 29]. In one study, not sharing of syringes was associated with consistent condom use, indicating that individuals are characterised by a broader risk taking profile [4].

There is a strong correlation between the reporting of receiving from and the passing of equipment to others [16]. Both sharing features are often part of the same injecting episode, and in addition, tit for tat cooperation rules may apply. Reporting of sharing is also correlated with the perception that peer norms condone needle sharing.

Unfortunately for those seeking to inform model parameters, the risk related questions posed to IDU are almost never quantitative in nature, as qualitative questions are thought easier to answer. Most questionnaires include only a yes/no question on sharing, or else introduce a limited number of answer categories (for example sharing never/occasionally/frequently/always [7]). Many of the studies are performed to enable assessment of the influence of an intervention on risk-behaviour. Publications therefore often, even where more quantitative raw data was gathered, report only whether a difference between the intervention groups (tested for statistical significance) was found [14, 57, 27].

A very important point to consider is in how far we can trust self-reported sharing estimates when these are available. IDU may feel social pressure to report less risky behaviour, and intoxication may impact memory. Ideally therefore, validity of risk-reporting should be corroborated by a more objective measure, such as disease incidence data.

Palmateer *et al* recently reviewed the evidence on the correlation between self-reported sharing of needles and HCV incidence [45]. Combining the results from twenty studies, they found that those who admitted having shared syringes were indeed much more likely to be infected with HCV compared to those denying having shared. However, they found that among the IDU reporting not or not recently sharing, the incidence rate of HCV could

still be as high as 19% per year. The pooled HCV prevalence among all the self-reported never-sharers was almost 60%.

The authors of the review argue that although sharing of other injecting equipment could explain some of the incidence among those reporting no syringe sharing, clearly under-reporting of risk-behaviour is common. Another indication for under-reporting is the relationship found between questionnaire length and the admitting of sharing; in one study 56% of IDU reported sharing when asked a single question, but when the same IDU were asked fifteen questions (for example distinguishing sharing between sexual partners and others) 75% admitted to sharing [58].

Corroborating the idea of risk heterogeneity, also prevalence and incidence rates of HIV and HCV have been shown to differ between ethnic groups, by type of drugs used, gender [13, 41, 51], or recruitment location, with those recruited from the street or injecting in prison at higher risk for infection [62]. Such research can only reveal a minimum in the actual risk heterogeneity however, as it can only quantify differences related to other measured variables. In conclusion, both self-reports on risk and incidence data do seem to indicate significant individual differences between IDU in their risk taking behaviour, but quantitative risk estimates are either lacking, or questionable.

Heterogeneity in risk over injecting time

Another important caveat in our knowledge is that the information on self-reported risk comes mostly from cross-sectional studies, which do not reveal how stable individual risk-behaviour is over time. Undermining the idea of individual stability in risk, it has often been shown that the rate of incidence of infection is related to the time since first injecting (or strongly correlated with this, individual age) [53, 62]. For example, in two studies those injecting for less than one year were found to have an HCV incidence rate respectively three [31] and four [48] times higher compared to more experienced injectors.

If risk-behaviour is highest for IDU early within their injecting career, it is especially important to reach IDU by interventions as quickly as possible. Alternatively, the drop in infection rate over injecting time may result from the fact that more experienced IDU often have been reached by intervention messages.

It is important to realise that the noted drop in incidence, as measured at group level, does not necessarily imply a change in risk-behaviour by the individuals. Instead, this drop may be a consequence of heterogeneity between individuals; those at risk for infection (not yet infected) at later injecting career times (among whom the infection rate is measured) will be those with least risk. Also, many of the studies that find this correlation may include ex-IDU or those that temporarily stopped injecting; new injectors do actively inject per definition, so that this fact only lowers risk estimates for those who have been injecting for longer.

A recent literature review aimed at estimating the time individuals inject drugs before permanently ceasing injecting or dying, and found this to vary from an average of around six years for IDU in Africa, to twenty-one years in South America [12]. Heterogeneity in this measure within populations could also be very important for Harm Reduction policy. For example, when there is a large sub-group of individuals that will quickly cease injecting independent of Harm Reduction efforts, it may be most efficient for intervention to target longer term injectors, who have shown not to cease injecting.

It is well known that individuals may often cease but then relapse to drug use [63, 64]. Self-reported risk and incidence are linked to such changeable variables as homelessness, incarceration, and relationship-status. If all IDU go through phases of higher and lower risk-behaviour with equal probabilities, then individual risk for infection averages out over

time. With a sufficiently high transition rate between the delineated risk groups, model predictions become similar to predictions made when assuming risk homogeneity (shown also in chapter 5 of this thesis).

However, proof for within individual heterogeneity in risk, over time of injecting, does not rule out that different individual risk types exist as well, distinguished by a lower or higher tendency to engage in sharing of equipment. Such between individual variability is expected to arise from differences in socio-economic status or psychological characteristics of the IDU. Substance addiction is often accompanied by mental health issues such as depression, schizophrenia and suicidality, and IDU suffering these psychiatric co-morbidities may have lower risk awareness or interest in self-preservation [50].

If longitudinal data is available, the existence of distinct individual types can be studied using statistical tools such as latent class or growth mixture modelling [20, 15]. For example, from data of drug users that had been followed for up to sixteen years, Hser *et al* identified three types; stably high level users, late decelerated users, as well as a small group of early quitters [20]. In another study Genberg *et al* distinguished five patterns of injecting drug use, described as persistent injecting, frequent relapse, early -, delayed -, and late cessation respectively [15]. It could also be shown that, compared to the other types, those that ceased injecting more often had a history of drug treatment and they less often used multiple substances. These statistical methods have so far not been used to study specifically IDU patterns of sharing behaviour over time, due to the lack of reliable longitudinal data on this measure.

A heterogeneity of questions remaining on risk of infection

Better estimates for the amount of sharing should be accompanied by better estimates for the risk of transmission per sharing event. Reliable data for this measure are lacking especially for HCV. In our models we set the probability for HCV-infection at 5% per use of a contaminated syringe, based on extrapolation from the number of infections that resulted from accidental needle stick injuries among health care workers [9]. Other modelling researchers have used estimates of 1% transmission per sharing event [18]. HCV may be more transmissible during the acute stage of infection, or when an individual is co-infected with HIV, but limited data are available on whether this is the case, and if so by how much.

Sharing of other equipment such as alcohol swabs, spoons and rinsing water may also lead to transmission of HCV, but, on the other hand, cleaning of injecting equipment might decrease the probability for infection [39]. Another complicating factor is that transmission probabilities for HIV and HCV can be affected by the type of syringe that is used [68].

It is further of great relevance not only to quantify for how long and how often IDU engage in sharing, but also who they share with. If higher risk individuals share most often with other high-risk individuals, this enables faster viral spread at the start of an epidemic, but eventual prevalence would be lowered (see chapters two and three of this thesis). As mentioned above, self-reported sharing was found to be related to social distance, with some IDU reporting sharing only with their sexual partners [56]. An important question is then also in how far we can maintain the assumption that sharing takes place with random other IDU within the risk sub-groups.

The impact of network structure, with individuals only connected to and able to infect a limited number of other individuals, has been much studied in the context of sexual diseases. One important consequence of sparseness in connections is slower initial spread of a virus. Network structure would also allow for different intervention strategies. For

example, sharing partners could be notified after diagnosis of infection [52]. However, models with many connections per individual, or with highly unstable connections over time, lead to similar dynamics as models with random mixing.

To study the network structure in hidden, difficult to reach or identify populations, respondent driven sampling methods were developed. In such studies participants are asked to recruit peers whom they know personally. One such study took place among Australian IDU [46]. These IDU were found to be highly connected, with fifteen being the median in the reported number of other known IDU seen within the last month. About 20% of the participants reported injecting with equipment received from their recruiter, this risk-behaviour related to ethnicity and social closeness between the IDU. From comparing characteristics of individuals with those of their recruiters however, it was concluded that connections were formed without much regard to demographic or drug use characteristics.

Heterogeneity in models

As argued above, both self-reported risk and disease incidence studies do indicate significant heterogeneity in risk-behaviour among IDU, but quantitative data on sharing frequency, that could be used to inform model parameters, are scarce. Often, studies using mathematical models also include estimation on risk variables, either from otherwise unpublished self-reported risk data, or from fitting of the model to observed viral prevalence and incidence. Here I briefly review several modelling studies that included diversity in risk among IDU, along with our own.

Raboud *et al* 2003 modelled the predicted impact of needle exchange programmes on the spread of HIV [49]. Based on not further specified self-reported risk data, they distinguished seven sub-groups in their model; non-sharers, IDU sharing with one steady partner, low-risk IDU sharing randomly, and IDU sharing up to five times more frequently compared to these low-risk IDU. Also, the higher risk IDU were more likely to make use of the needle and syringe exchange programme, which enhanced the model intervention effects.

Vickerman *et al* 2007 modelled the impact of reducing syringe sharing among London IDU [66]. The average syringe sharing rate was based on the amount of distributed syringes and the reported syringe re-use and injection frequencies. Remaining risk-behaviour parameters were fit to HCV prevalence over time injecting. This data showed rapid spread of HCV among new injectors, which could be reproduced by several distinct model types; either all new injectors shared much more frequently, or a large sub-group of high-frequency sharers existed, or HCV was much more transmissible during acute infection. The importance of being able to distinguish these assumptions was stressed, since the different model types led to very different projections for the future spread of disease and for impact of intervention.

Hahn *et al* 2008 modelled the hypothetical effects of HCV vaccination strategies [18]. Basing most risk parameters on self-reported behaviour, they included separately the sharing of syringes and of other equipment, and they distinguished three risk sub-groups. Qualitative data was translated to quantitative data. For example, to obtain a syringe sharing frequency, the reported injecting rate was multiplied by 75% for those indicating that they usually shared syringes. For those reporting never sharing any syringes or equipment however, an equipment sharing rate was included as well, to enable the model to reproduce the incidence rate among these IDU. HCV incidence was impacted most when targeting high-risk IDU for vaccination.

Rolls *et al* 2011 build a static undirected network model, based on Australian data

[52]. The modelled network represents an actual network found by respondent driven sampling. Since the network otherwise became too sparse for viral spread, the network was based on used with rather than shared needles with data, and model IDU also had a probability of becoming infected from outside of the network. From one to six connections were reported by the IDU. In the model the rate of re-infection was found to be higher than the rate of primary infection, which was explained by the boomerang effect; IDU that clear HCV-infection may be re-infected by connected IDU whom they themselves had previously infected. The authors also note that it takes longer for HCV to spread over the network structure compared to assuming a fully connected graph.

In two separate studies in 2012 and 2013, Vickerman *et al* used the same basic model [69, 70]. Their first article addresses whether we can understand how HCV and HIV prevalence relate to each other, the second what HIV to HCV prevalence may tell us about the degree of sexual spread of HIV among IDU. All behavioural parameters were given wide ranges, both to encompass different populations, and since, as the authors state, there is much uncertainty in risk-behaviour. The model contains two risk sub-groups, with up to 60% of the IDU sharing syringes up to ten times as frequently compared to the remaining IDU. Additionally, sharing could preferentially occur within the risk sub-groups, and the IDU could transition between the groups. The estimate for the relative amount of sexual spread of HIV was impacted by these assumptions on the population risk distribution. Projected intervention effects were also found to be influenced by risk heterogeneity.

All of the above outlined studies exemplify the importance of including heterogeneity in risk-behaviour when modelling the spread of infection among IDU. Also, they show the diverse ways of describing this heterogeneity. In our own models we included two sub-groups of IDU distinguished by their syringe sharing frequency. For informing on this risk-behaviour, we also used both self-reported risk data and data on viral prevalence and incidence.

We first estimated risk heterogeneity from self-reported behavioural data from the Amsterdam Cohort Studies (ACS) among injecting drugs users (chapter two of this thesis). By assuming a Poison distributed sharing process we could fit a grouped model to the questionnaire answers as to when individuals had last borrowed a syringe. We excluded however for this analysis those IDU who reported never having shared, assuming the high HCV prevalence among these IDU to indicate false reporting. In effect, as in the studies conducted by Hahn [18] and Rolls [52] mentioned above, we compensated for presumed under-reporting of risk-behaviour. By this method, we estimated that about 60% of IDU shared just over once per two months, and remaining IDU about five times each month.

We also obtained risk estimates by fitting our individual-based model to HIV and HCV prevalence and incidence as measured by the ACS over time (chapter three of this thesis). Consistent with the magnitude of the above estimates, a good fit with this data was achieved by assuming 70% of IDU to share around one syringe per two months, and remaining IDU to share six syringes per month. Also, we assumed that 70% of sharing occurred preferentially within the risk-sub-groups, as we could otherwise not reproduce the very quick initial spread of HIV.

This modelled risk distribution was important in allowing us to explain the epidemic trends among the Amsterdam IDU. However, as in the modelling study on London IDU by Vickerman [66], we also found that multiple model types could fit the Amsterdam data. Hypothetically, by knowing the true risk-behaviour distribution, we could more properly quantify the natural population risk decline, by especially the high-risk IDU having died of HIV. This in turn would allow for a better estimate of the role Harm Reduction played in

lowering IDU risk-behaviour over time. Our estimates for the variability in syringe sharing also impacted our predictions for the effects of treatment as prevention (chapters four till six of this thesis).

New ways of informing on heterogeneity in risk

Clearly, better quantitative data on the risk-behaviour distribution among IDU would improve predictions from modelling studies. Other methods, not relying on self-reports, have been developed to inform on the risk structure within populations. These cleverly make use of how the risk distribution impacts on the way infections disperse through a population.

Sutton *et al* used the fact that where risk-behaviour is more heterogeneous, more co-infections will occur [60, 61]. The same behaviour, i.e. more frequent sharing of injecting equipment, increases individual risk for both HIV and HCV, but also for Hepatitis B Virus infection. Their model was fitted separately to infection data of different regions, and additionally allowed for increased risk-behaviour during the first year of injecting. Total incidence, and therefore the estimated average risk, differed much between the regions. The risk-behaviour distribution was assumed to follow a gamma distribution; it was estimated that around 60% of IDU were at less than average risk for infection, while in the different regions 5% to 15% experienced over twice the population average risk.

Castro Sanchez *et al* used data on the prevalence of HIV and HCV over time since first injecting [6]. Among the parameters of the model they fit to this data are those for heterogeneity in risk-behaviour, but they simultaneously address uncertainty in several other parameters, including the increase in susceptibility for HCV-infection when co-infected with HIV and the average time to quitting injecting drug use. They compared models with one, two or three risk groups, and also considered both random mixing and the possibility for more stable sharing partnerships. In their analysis the random mixing two grouped model was found optimal, since more complicated model structure did not significantly improve the model fit. In the majority of their best fitting models, the higher risk IDU shared between 30 and 50 times more often compared to the low-risk IDU, with these low-risk IDU making up between 30% and 95% of the population.

There are promising new methods which elucidate on population structure by combining genetic viral data with epidemiology. For example, Sacks-Davis *et al* studied genetic clustering related to social networks of IDU [54]. To my knowledge however, such methods have not yet been used to elucidate on heterogeneity in level of risk-behaviour within IDU populations. Alam *et al* studied spread of HIV among men who have sex with men [1]. They relate size distribution of genetic clusters to the tendency for the individuals to periodically engage in much higher risk-behaviour. They note how such episodic high-risk will render undirected test and treat interventions much less effective, rendering instead partner notification or directed counselling services much more useful.

Magiorkinis *et al* combined information on viral phylogenies with epidemiology to estimate the diversity in the number of infections by HCV infected individuals [30]. Their method relies on the fact that when most infections are caused by only a small subset of infected individuals, genetic drift will be much lower compared to when all individuals contribute to disease spread equally. For the risk of spreading infection the authors assumed a zero inflated Poisson distribution. The method also relied on estimates of the average time between infections (the generation time) during the early epidemic (the exponential growth phase). The authors studied the HCV epidemic in the overall Greek population, during which about one-fourth of all HCV-infections had been among IDU. They estimated that 80% of all new infections had been caused by less than one third

of the infected individuals. This large heterogeneity in transmission risk was explained by the fact that in the past infected individuals could engage in paid blood transfusion donations.

Future perspectives

Better estimates of risk-behaviour heterogeneity

From fitting mathematical models to incidence and prevalence of viral infections, risk-behaviour can be estimated. However, uncertainty in estimates quickly increases when multiple variables are unknown, in which case quite different assumptions may fit well to the epidemic data. Risk-behaviour estimates will therefore improve also when better information becomes available on disease variables, including the transmission probabilities per sharing event. Estimates are further improved by combining information from multiple infections. Models of IDU populations can be fit as we did simultaneously to HIV and HCV, but for example also to the spread of Hepatitis B Virus.

Genetic analysis of viral infections is becoming more affordable. In future, the methods combining genetic data with epidemiological models will enhance our insights into the effective heterogeneity in risk-behaviour among IDU. Such methods can also address variability in risk within individuals over time since start injecting. This will allow better predictions of epidemic spread, and of the benefits expected from implementing interventions. However, such methods will depend crucially on a set of assumptions, often including the type of distribution which describes the risk heterogeneity.

Despite the noted tendency for under-reporting, self-reported behavioural and incidence data will remain of utmost importance. Such data can be linked to other measurable variables, for example injecting location, socio-economic status, gender or ethnicity. Only this kind of information will allow the targeting of interventions to IDU with certain sharing behaviour. Especially longitudinal data on risk-behaviour is needed, which could also be studied for evidence of the existence of distinct risk types.

Ideally, to improve the utility of the self-reported risk data for modelling studies, modellers should be more involved in the process of data gathering, such as questionnaire development. Of principal importance will be the posing of more quantitative questions; for model parametrisation information on the frequency of sharing is needed. By such closer collaboration with those working with the IDU, mathematical modellers would also gain an enhanced insight into the real life behaviours that affect disease spread, and of the reliability of the collected data.

Researchers have long called for a standardisation of data gathering methods among IDU, in order to ensure the quality of the gathered data, and also to enable comparison between different IDU populations [3]. Such comparison is compromised by differences in the wording and definitions, but also the time frame of questions; e.g. IDU may be asked whether they shared within the past year, within the past week, or ever [58].

One attempt at standardisation is represented by The Blood-Borne Virus Transmission Risk Assessment Questionnaire (BBV-TRAQ), which includes a quantitative question on syringe sharing [59]. Interestingly, merely administering this questionnaire seemed to lower risk-behaviour, perhaps as it increased interviewee awareness of behaviour [65]. Although translated by the World Health Organisation into eight languages however, this questionnaire is still far from universally accepted as a standard. Changing questionnaires would be a drawback in serial surveys and already running cohort studies.

Often, IDU are recruited for studies at for example a syringe exchange programme

site. To obtain a more representative sample of IDU, respondent driven sampling may be used, with participating IDU themselves recruiting peers [26, 46]. Even such studies may be biased, however, if IDU differ in their willingness to participate. Recently more such studies are being performed, also with the aim of gaining more insight into injecting networks. For our models, knowledge is needed as to how strongly connected the IDU are, and whether sharing is more likely between IDU with like risk-behaviour.

The right amount of risk-behaviour heterogeneity in models

Ever more detailed information could eventually be included in individual-based simulation models, including specific network or spatial structure. With the advance of computing powers, we are no longer constrained to simulations of only small populations [35, 43]. This even enables addressing multiple high-risk populations at the same time, including besides the drug users for example sex workers, prisoners, men having sex with men and how these groups overlap. The goal of such models is to capture all possibly relevant aspects of disease spread, to enable precise predictions of the future course of an epidemic, so that the effects of possible interventions can be properly quantified.

However, much like the reality that they simulate, such highly complex models may be very difficult to interpret. In simpler models, the link between the different assumptions and model outcome is much more direct. This makes such models more helpful in clarifying our thinking about the processes that determine viral spread, possibly inspiring novel ideas for interventions and future studies. Therefore, less detailed models will also remain important in future.

Adding more detail in models may also be useless unless good estimates for parameters are available [21]. As argued above, we expect that better risk information will become available, due to the use of new methods using genetic data, and by more rigorous gathering of self-reported risk data. However, the information will never be complete, and population risk structure is also likely to be distinct for different populations. Especially outside of the developed world, costs will restrain research. The behavioural investigations in such populations should then be guided by the behavioural assumptions that are found to most strongly impact model predictions.

As recounted above, there are diverse ways of modelling heterogeneity in risk-behaviour. We made relatively simple assumptions, including only two risk sub-groups of IDU. Arguably however, this simple structure captures all the most essential aspects of risk heterogeneity; quicker initial viral spread, greater difficulty in eradication of a disease, a variable HIV to HCV prevalence ratio, and the possibility of targeting interventions by risk-level. Allowing IDU to switch between risk-levels would only diminish the effects of risk heterogeneity (chapter five of this thesis). Including more risk groups or a smooth risk distribution would also not be expected to impact on qualitative model aspects.

Addition of network structure could impact model behaviour substantially [10]. It slows initial viral spread, and also allows for different interventions, such as partner notification. For certain research questions then, it will be important to study IDU network models. However, IDU may usually engage in sharing with many other IDU [46], and their sharing connections may be highly unstable over time. If this is the case, an assumption of random sharing well approximates their behaviour. The importance of including detailed network information in models should be investigated by comparing models with an without network structure.

Our models might further improve by inclusion of heterogeneity in risk-behaviour over time since first injecting. An important question to investigate further remains whether or not IDU commonly engage in highest risk-behaviour when they start injecting [8]. More

speculatively, if in future research different types of IDU can be identified, with different patterns of drug use and risk-behaviour over time, models might be improved by inclusion of such IDU types. In these models, risk-behaviour could perhaps be linked to other relevant demographical variables, such as gender, age or mental co-morbidities. Using such models could aid the designing of specific intervention strategies, more tailored to the individual needs of IDU.

In conclusion, we cannot dictate on a general right amount of complexity in the description of risk-behaviour for future studies on infection spread among IDU. Instead, the injecting equipment sharing behaviour should depend on the research question of the model study, and on the data which is available. However, although relatively simple risk description may often be sufficient, ignoring variability in risk-behaviour altogether would certainly limit the applicability of model results.

A growing variety of interventions

To stem the tide of viral infections, the health care community is ever working on new interventions. As described above, developments in HCV treatment could benefit IDU in the immediate future. Recently, there has been much debate on the use of Pre-Exposure Prophylaxis, which lowers the probability of acquiring HIV-infection when taken before exposure to HIV [2]. Studies are advancing on effective vaccines against HIV and HCV [73, 18]. Research for a cure of HIV is also on-going [33].

Mathematical modelling work will be very important for guiding the dissemination of these treatments and vaccines, by prediction of their consequences at population level [24, 5]. A challenge for modellers will be to consider the interactions between the different Harm Reduction measures and such interventions [34]. For example, Harm Reduction may decrease the risk for re-infection after successful HCV treatment, potentially increasing treatment usefulness [38]. Additionally, interactions between viral infections should be addressed further. For example, HIV co-infection lowers the success rate of treatment for HCV, so that high HIV prevalence lowers the population level benefits of HCV treatment.

Models have had great impact on policy in the past. The idea of treatment as prevention first gained wide interest after a modelling study suggested its potential in reducing HIV incidence [19]. The concept is now part of the guidelines of the World Health Organisation, in the form of recommendations to treat HIV infected individuals earlier after their diagnosis [32]. We found that expanded treatment could also benefit IDU populations, if infected IDU are identified and put on treatment soon after their infection. Otherwise, since HIV is spread efficiently by shared syringes, high-risk IDU will still infect many others.

For HCV also, the concept of treatment as prevention is promising [37, 36]. We showed how, in a low HCV prevalence setting, first treating highest risk IDU could prevent by far the most new infections. At high HCV prevalence, however, benefits of treating high-risk IDU may be limited, due to their high likelihood to be re-infected, in which case treating low-risk IDU may be most prudent. For this question of who to treat first, prevalence of viral contamination among exchanged syringes, rather than viral prevalence among IDU, is most informative. This prevalence among syringes could be measured for example, where available, at needle and syringe exchange facilities. However, the potential for bias in such a measurement, as not all IDU use such facilities, should be kept in mind.

Heterogeneity in risk-behaviour matters. We showed that the variability in injecting risk-behaviour among IDU has significant consequences for the expected spread of infections. In future models, these effects should be explored further. Importantly, we showed that underestimating variability in risk could lead to overly optimistic expectations

from interventions. However, we also stress that awareness of heterogeneity represents an opportunity to improve interventions. By differentially targeting IDU, Harm Reduction policy could be made more effective and cost-efficient.

We also emphasize the importance of demographical changes in IDU populations. Depending on availability of drugs, social trends and other factors, fewer or more individuals may start injecting drug use over time. We showed that, especially for a declining IDU population, treatment as prevention will have little effect on incidence, unless it is implemented already at the start of an HIV outbreak.

An important task for modellers is also the proper assessment of the effects Harm Reduction policy has had in the past. We could explain most of the observed decline in spread of HIV and HCV among IDU in Amsterdam by taking into account the ageing and decline of this population, combined with especially high-risk-behaviour IDU having died of HIV. This study thereby serves as a warning for future research which attempts to relate trends in viral incidence and prevalence to effects of Harm Reduction policy [67]. For a fair assessment of intervention impact, the natural progression of epidemics, the effects of heterogeneity in risk-behaviour, as well as changes in demography, may not be ignored.

With the creation of improved models, which incorporate more sound data on risk-behaviour and disease variables, I expect our model predictions to become more reliable in future. In models, we can easily achieve elimination of HIV and HCV, for example by assuming a perfect intervention which stops all equipment sharing. In reality, this goal is not easy to reach. However, with scaling up of HCV treatment among IDU, the hopes for future vaccines and a cure for HIV, combined with those Harm Reduction efforts that have proven effective in the past, gaining control over the spread of HIV and HCV no longer seems impossible. By guiding the most optimal use of a combination of interventions, modelling will contribute to the eventual elimination of HIV and HCV, even among IDU and other high-risk sub-populations.

Heterogeneity in references

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Samenvatting in het Nederlands

Hoofdstuk 1

Met Harm Reduction wordt beleid bedoeld dat als doel heeft om de schade te verminderen die drugsgebruikers aan de maatschappij en zichzelf toebrengen. Dit houdt onder meer in het adviseren van drugsgebruikers en het aan hen verstrekken van schone spuiten of substitutie therapie (zoals methadon), om zo de verspreiding van bloed overdraagbare ziekten tegen te gaan. Een ziekte die zich sterk verspreidt onder injecterende drugsgebruikers (IDU) is Hepatitis C (HCV); deze ziekte kan levercirrose en levercarcinoom veroorzaken. Ook het virus dat tot AIDS leidt, HIV, verspreidt zich via gedeeld injectie materiaal. Door het maken van mathematische modellen kunnen we inzicht geven in de te verwachten verspreiding van deze ziekten onder IDU, wat helpt om het preventie beleid te verbeteren.

Hoofdstuk 2

We maakten eerst een deterministisch model van de verspreiding van zowel HIV als HCV onder IDU. Zowel HIV als HCV prevalentie hangt af van het risicogedrag van de IDU; als er meer spuiten worden gedeeld, dan raken er uiteindelijk ook meer individuen besmet. Omdat HCV ongeveer tienmaal zo besmettelijk is via bloed-bloed contact als HIV, is de HCV prevalentie hoger, en heeft bijna elke populatie drugsgebruikers een percentage hepatitis C geïnfecteerde individuen. Daarom werd gesuggereerd dat in populaties van IDU de HCV prevalentie een maat kan zijn voor het risico op uitbraak van een HIV epidemie.

We berekenden de R_0 voor HIV, dat is het verwachte aantal nieuwe HIV gevallen dat een enkel HIV geïnfecteerd individu zou veroorzaken in een volledig vatbare populatie, waarbij een R_0 groter dan één duidt op de potentie voor een HIV uitbraak. We vonden dat het voor de verwachte HIV ten opzichte van HCV ratio erg belangrijk is hoe het risicogedrag verdeeld is in de populatie. Voor een bepaalde endemische HCV prevalentie geldt: hoe heterogener de mate van delen van injectie materiaal, en hoe waarschijnlijker individuen delen met iemand van hun eigen risiconiveau, hoe groter de potentie voor verspreiding en de te verwachten prevalentie van HIV.

Om risico-gedrag ten behoeve van het model te bepalen, hebben we zelf-gerapporteerde gedragsinformatie van de Amsterdamse Cohort Studies (ACS) van injecterende drugsgebruikers geanalyseerd. Meer specifiek hebben we een model met risicogroepen gefit aan antwoorden op de vraag "wanneer heb je voor het laatst met een geleende spuit geïnjecteerd?". Hierbij vonden we dat er grote heterogeniteit was in risicogedrag; in onze beste fit op deze data deelde ongeveer een derde van de populatie ongeveer zeven maal zo vaak spuiten als de resterende IDU.

Hoofdstuk 3

In de laatste decennia zijn onder IDU in verschillende landen, waaronder in Nederland, de incidentie van HCV en vooral ook de incidentie van HIV sterk afgenomen. Er is echter geen duidelijkheid in hoeverre dit veroorzaakt is door Harm Reduction beleid, omdat er tegelijkertijd andere grote veranderingen zijn geweest. Zo zijn er in Amsterdam in recente jaren relatief minder nieuwe injecterende drugsgebruikers bijgekomen, waardoor de gemiddelde leeftijd van de drugsgebruikers sterk is toegenomen. Voor Amsterdam probeerden we te bepalen welk deel van de afname van HIV en HCV incidentie wordt verklaard door het beleid en de hulpverlening in Amsterdam, en welk deel door veranderingen van de populatie zelf.

We maakten een model van de epidemieën van HIV en HCV onder injecterende drugsgebruikers in Amsterdam in de afgelopen vijftig jaar. Dit is een individu gebaseerd model; elk individu heeft per tijdstap een kans om besmet te raken of te sterven, en ook eigenschappen zoals leeftijd en tijd sinds HIV-infectie worden elke maandelijkse tijdstap bijgewerkt.

Parameters zoals de leeftijdsverdeling van nieuwe injecterende individuen, de kans om te stoppen met injecteren, en de sterftekans (afhankelijk van leeftijd en huidig drugsgebruik), werden gebaseerd op data van de Amsterdamse Cohort Studies (ACS). Dit is een van de langst lopende drugsgebruiker studies die tot nu zijn uitgevoerd. Het verzamelen van individuele data, waaronder HIV en HCV status, begon al in 1985, slechts enkele jaren na de eerste HIV infecties onder de Amsterdamse IDU. Het aantal nieuwe individuen dat de populatie binnenkwam werd gebaseerd op data van de spuitomruil en de centrale methadon registratie. Data van een samenwerkingsverband met meerdere cohorten (CASCADE) werd gebruikt voor het bepalen van een additionele HIV sterfte onder IDU, afhankelijk van leeftijd en tijd sinds HIV infectie.

Risicogedrag van de IDU in het model werd gebaseerd op de model fit met de prevalentie en incidentie gegevens van HIV en HCV van de ACS. Een goede fit werd alleen bereikt door ongeveer een derde van de individuen een veel (tienmaal) hogere frequentie van delen van injectiemateriaal te geven ten opzichte van de resterende IDU, en daarmee dus meer kans om besmet te raken met beide ziekten. Om in het model ook de geobserveerde snelle initiële toename in HIV te bereiken, hebben we bovendien aangenomen dat de IDU relatief vaak deelden met individuen met vergelijkbaar risicogedrag.

Het was niet nodig verandering van risicogedrag over de kalendertijd aan te nemen om met het model de geobserveerde grote dalingen in HIV prevalentie en HIV en HCV incidentie te reproduceren. De lichte daling in HCV prevalentie werd wel alleen op deze wijze verkregen. Dat wil zeggen dat we op basis van dit onderzoek niet hebben kunnen aantonen dat Harm Reduction beleid in Amsterdam grote effecten heeft gehad. Alhoewel het risicogedrag van de IDU wellicht wel afnam door het beleid, is waarschijnlijk veel van de afname in incidentie al veroorzaakt door de veroudering van de populatie en het natuurlijk verloop van de epidemieën. Hierbij is vooral belangrijk dat de mensen met het hoogste risicogedrag als eerste besmet raakten en overleden aan HIV.

Hoofdstuk 4

Recentelijk wordt veel hoop gevestigd op het gebruik van antiretrovirale therapie van HIV geïnfecteerden als preventiemiddel. De therapie is ontwikkeld om HIV morbiditeit te verminderen, maar door middel van verlaging van HIV virusconcentratie in het bloed heeft de therapie als bijeffect een verminderde kans tot overdracht van infectie. Het hierboven beschreven individu gebaseerde model bood ons de mogelijkheid om te kwantificeren in

hoeverre therapie in het verleden de HIV epidemie onder de Amsterdamse IDU heeft beïnvloed. Door de demografie van de gemodelleerde populatie aan te passen, konden we vervolgens bestuderen hoe ook in andere situaties de frequentie van behandeling invloed zou kunnen hebben op de HIV incidentie onder IDU.

Door uitkomsten van ons model met en zonder toevoeging van HIV therapie te vergelijken, concluderen we dat HIV therapie in het verleden nauwelijks invloed heeft gehad op de HIV incidentie onder de Amsterdamse IDU. De IDU onder behandeling waren minder infectieus, maar dit effect werd gecompenseerd door het feit dat deze individuen langer bleven leven, en dus ook langer andere IDU konden besmetten.

Vroeger begon men behandeling meestal pas in een gevorderd ziekte stadium van de infectie. Een behandeling van IDU in een eerder ziekte stadium zou wel veel invloed kunnen hebben op verspreiding van het virus, waarvoor de IDU ook voldoende vaak zouden moeten worden getest. Bijvoorbeeld, als de IDU gemiddeld vanaf één jaar na hun HIV infectie worden behandeld, vonden we dat de totale incidentie over de eerste dertig jaar van een HIV epidemie ongeveer kon worden gehalveerd. Echter, om de behandeling veel effect te laten hebben is het ook van groot belang dat de behandel strategie al in de eerste jaren van een HIV epidemie kan worden opgezet. Dit laatste geldt vooral sterk wanneer een IDU populatie afneemt in grootte, door een verminderde instroom van nieuwe injecterende individuen.

We onderzochten ook de effecten van de interventie op incidentie voor populaties met een andere risicostructuur. Als belangrijk punt kwam hierbij naar voren dat het simpelweg aannemen dat alle IDU gelijk zijn in hun risicogedrag, in plaats van het aannemen van een meer realistisch niveau van risicoheterogeniteit, leidde tot een grote overschatting van de te verwachten voordelen van therapie verstrekking.

Hoofdstuk 5

De bovengenoemde modelstudies leerden ons dat risicogedrag waarschijnlijk sterk varieert tussen IDU, en dat deze heterogeniteit impact zal hebben op de effecten van Harm Reduction beleid. Het beleid hierop aanpassen zou mogelijk ook het beleid kunnen verbeteren; de interventies zouden specifiek kunnen worden gericht op IDU van bepaald risiconiveau, waardoor er meer effect zou kunnen zijn per bereikte IDU.

We gebruikten eerst een deterministische model van HCV en HIV verspreiding onder IDU om de effecten van gerichte interventie te onderzoeken. Voor deze analyse bevatte het model twee risico sub-groepen, die verschilden in de frequentie van delen van spuiten. We simuleerden ongerichte interventie, en interventie gericht op degenen met het meeste, of juist diegenen met het minste risicogedrag. We onderzochten twee typen van interventie, namelijk verstrekking van schone naalden aan een groep van IDU, en isolatie of opium substitutie therapie; dat laatste geïmplementeerd als het geheel stoppen van risicovol injecteer gedrag door individuen.

Voor een beter begrip hoe risicogedrag het effect van interventie bepaalt, ontwikkelden we ook een berekening van de voordelen van interventie per individu. Deze voordelen omvatten ten eerste de kans dat de interventie infectie voorkomt voor het individu onder interventie. We telden daarnaast bij de voordelen het aantal infecties dat we verwachtten te voorkomen van deze IDU naar andere IDU, door het verminderd delen van injectie materiaal.

We vonden dat het richten van interventies op bepaalde sub-populaties van IDU het beleid inderdaad veel effectiever zou kunnen maken per uitgedeelde spuit of per bereikte IDU. Wie echter het best benaderd kunnen worden bleek af te hangen van de ziekte en

de omstandigheden. Misschien tegen-intuïtief is het soms het beste om vooral de laag-risico IDU te benaderen. Mensen met hoog risicogedrag, die vaak injectie materiaal delen, zullen veelal al besmet zijn met HCV voor ze kunnen worden bereikt door Harm Reduction interventies. Daarom kan men deze ziekte wellicht vaker voorkomen wanneer men zich richt op individuen met minder hoog risicogedrag, waarvan een groter aandeel nog niet geïnfecteerd zal zijn.

We vonden dat in het algemeen meer HIV infecties voorkomen worden wanneer men zich richt op de individuen met het hoogste risicogedrag. Het verschil met HCV wordt verklaard door de minder efficiënte verspreiding van dit virus, zodat voordat ze worden bereikt door interventie, zelfs de hoog risico IDU meestal nog niet met HIV besmet zullen zijn.

Hoofdstuk 6

HCV kan worden genezen door middel van antiretrovirale middelen. Door de bijeffecten en de relatief lange behandelduur van de huidige standaardtherapie, en ook de mogelijkheid van re-infectie met HCV, zijn hiermee echter tot dusverre nog maar weinig IDU behandeld. Sinds zeer kort zijn zijn er betere maar ook erg dure middelen beschikbaar; deze verkorten de behandelduur en geven een veel hogere kans op slagen van de therapie.

Genezing van HCV zal in directe zin gezondheidsproblemen van het behandelde individu voorkomen, maar ook de verdere verspreiding van HCV naar anderen stoppen. Nieuwe infecties worden vooral voorkomen door mensen te genezen die de meeste infecties zouden hebben veroorzaakt, dus diegenen die het vaakst hun injectie materiaal delen. Echter, her-infectie met HCV is ook het meest waarschijnlijk voor deze IDU met hoog risicogedrag. We onderzochten daarom wie het beste eerst worden behandeld, degenen met hoger of juist degenen met lager risicogedrag.

We gebruikten een methode van kansberekening voor de voordelen op populatie niveau per behandeling van één IDU. Behandeling kan leiden tot succesvolle genezing van een individu, maar dit voordeel wordt verminderd met de kans op re-infectie. We voegden bij de voordelen het verwachte aantal voorkomen infecties naar andere IDU toe. Dit totaal aan voordelen werd bestudeerd als functie van risicogedrag, de mate van delen van spuiten, door de behandelde IDU.

Wie het beste behandeld kunnen worden voor HCV bleek af te hangen van de HCV prevalentie onder de gedeelde spuiten; wanneer meer dan de helft van alle gedeelde injectiespuiten HCV besmetting droeg, was re-infectie zo waarschijnlijk voor hoog risico IDU dat behandeling van mensen met weinig risicogedrag het meest zinvol bleek. Bij prevalentie lager dan vijftig procent onder de gedeelde spuiten echter, leverde het meer voordeel op om eerst de mensen met hoog risico te behandelen, omdat dit meer infecties naar anderen voorkwam.

Hoofdstuk 7

Het bovengenoemde probleem betreffende de meest efficiënte distributie van HCV behandeling werd verder bestudeerd met behulp van een deterministisch populatie model. Dit deterministische model stelde ons in staat enkele additionele aannamen te maken, zoals partiële immuniteit tegen re-infectie voor de eerder geïnfecteerde individuen.

Gebruik makend van dit populatie model konden we ook onderzoeken hoe de HCV prevalentie onder de gedeelde injectiespuiten samenhangt met de HCV prevalentie onder de IDU. We vonden dat hoe meer heterogeen een IDU populatie is ten aanzien van

risicogedrag, hoe meer de HCV prevalentie onder de gedeelde spuiten hoger zal zijn ten op zichten van de virale prevalentie onder de IDU.

Voor de vraag op wie behandeling het beste gericht kan worden vonden we geen grote effecten van de toegevoegde details in dit model. Ook de verwachte veranderingen in de behandelduur en de kans op slagen van de behandeling bleken niet van invloed op deze vraag. Bij minder dan ongeveer vijftig procent prevalentie onder de gedeelde spuiten verminderde de behandeling van hoog-risico IDU de HCV prevalentie het meest. Boven dit niveau van prevalentie bleek behandeling van laag-risico IDU juist voordeliger.

We voegden ook een risico-verminderende interventie toe aan de HCV behandeling. Deze combinatie van interventies werd tot op hogere niveaus van de HCV prevalentie het beste gericht op de hoog-risico IDU.

Hoofdstuk 9

Heterogeniteit in risicogedrag is van belang. Het beïnvloedt het natuurlijk verloop van de verspreiding van infectieziekten onder injecterende drugsgebruikers, en ook de impact van Harm Reduction beleid hierop. Zoals hierboven benadrukt, kunnen modellen zonder gedrags-heterogeniteit een te optimistisch beeld schetsen van de te verwachten resultaten van een interventie. Tegelijkertijd biedt herkenning van de heterogeniteit een kans; interventies kunnen mogelijk efficiënter worden gemaakt door een meer gerichte aanpak. Er is nu echter een gebrek aan betrouwbare informatie over de daadwerkelijke risicoverdeling in populaties van IDU.

Risicogedrag kan op verschillende manieren worden gemeten. Risicogedrag kan worden afgeleid van de verspreiding van infectieziekten, waarbij vooral de gezamenlijke verspreiding van HIV en HCV ons kennis oplevert. Nieuwere methoden maken gebruik van viraalgenetische data, in combinatie met epidemiologische modellen. Veel is ook bekend door het bevragen van de IDU zelf. Een nadeel is dat hierbij wel vaak sprake lijkt te zijn van onderrapportage van risicogedrag; ook veel van de mensen die zeggen nooit injectiespuiten te delen zijn toch besmet met HCV. Zelf-gerapporteerde data is vaak ook kwalitatief van aard (ja/nee), terwijl voor modellen kwantitatieve gedrags-gegevens noodzakelijk zijn. Een groot voordeel van zelf-gerapporteerd risicogedrag is dat het aan andere variabelen kan worden gelinkt, bijvoorbeeld aan geslacht of de omgeving waar wordt geïnjecteerd, wat belangrijk is voor het mogelijk meer gericht kunnen inzetten van de interventies.

Naast het belang van heterogeniteit in risicogedrag, lieten we zien dat ook demografische veranderingen in IDU populaties niet genegeerd mogen worden, wanneer men de effecten van Harm Reduction beleid onderzoekt. Met behulp van onder meer betere gedrags-gegevens, kunnen model-simulaties in de toekomst meer betrouwbaar zijn. Door de toename in rekenkracht van computers is er een grote toename in de complexiteit van epidemiologische modellen mogelijk. De modellen zijn vaker individu gebaseerd, en bevatten soms zelfs specifieke bepalingen over wie met wie deelt. In onze relatief simpele modellen met slechts twee gedragstypen, zijn echter waarschijnlijk de belangrijkste effecten van heterogeniteit in risicogedrag al aanwezig. Een groot voordeel van simpelere modellen is dat ze ons een beter inzicht geven in de causale verbanden met betrekking tot infectieziekten verspreiding.

In de nabije toekomst zullen waarschijnlijk meer IDU effectief worden behandeld voor HCV, en voor de langere termijn is er hoop op vaccinaties en zelfs op genezing van HIV. Het zal voor modelleurs een uitdaging zijn om ook de interacties van deze en de verschillende soorten Harm Reduction interventies juist te bepalen. Modellen zullen helpen om in de toekomst de interventies doeltreffender te maken, en daarmee, uiteindelijk, om de verspreiding van HIV en HCV via gedeelde drugsspuiten te stoppen.

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List of publications and conference presentations

Research included in this thesis, by topic:

de Vos AS, van der Helm JJ, Prins M, Kretzschmar MEE. Determinants of persistent spread of HIV in HCV-infected populations of injecting drug users.
- Published in Epidemics 2012; 4:57-67.
- First results for this topic were presented on a poster at the NCHIV 2010 in Amsterdam.
- An oral presentation was given at the key populations symposium, a satellite to the the ISSTDR 2011 conference in Qubec City, Canada.

de Vos AS, van der Helm JJ, Matser A, Prins M, Kretzschmar MEE. Decline in incidence of HIV and hepatitis C virus infection among injecting drug users in Amsterdam; evidence for harm reduction?
- Published in Addiction 2013; 108:1070-1081.
- An oral presentation of this subject was given at the AIDS 2012 conference in Washington DC, USA.

de Vos AS, Prins M, Coutinho RA, van der Helm JJ, Kretzschmar MEE. Treatment as prevention among injecting drug users; extrapolating from the Amsterdam cohort study.
- Published in AIDS 2014; 28:911-918.
- Presented as poster at the NCHIV 2013 in Amsterdam.

de Vos AS, Kretzschmar MEE. The efficiency of targeted intervention in limiting the spread of HIV and Hepatitis C Virus among injecting drug users.
- Published in J Theor Biol 2013; 333:126-134.
- First results for this topic were presented on a poster at the NCHIV 2012 in Amsterdam.

de Vos AS, Kretzschmar MEE. Benefits of Hepatitis C Virus Treatment: A balance of onwards transmission prevention and re-infection.
- (under review).
- A poster entitled "A method to explore the benefits of targeted intervention" was presented at EPIDEMICS 4, Amsterdam, 2013.

de Vos AS, Prins M, Kretzschmar MEE. HCV treatment as prevention among IDU: who should we cure first?
- (under review)
- Orally presented at the 3rd International Symposium on Hepatitis Care in Substance Users, INHSU 2013, in Munich, Germany.

de Vos AS, Kretzschmar MEE. The various ways of modelling and measuring variability in risk behaviour among Injecting Drug Users.
- A poster of this topic was presented at the WEON 2013 in Utrecht, and at the INHSU 2013, in Munich, Germany.

Earlier research:

Claessen, D, **de Vos AS**, de Roos, AM. Bioenergetics, overcompensation and the source/sink status of marine reserve. Can J Fish Aquat Sci. 2009; 66:1057-1071.

Althaus CL, **de Vos AS**, De Boer RJ. Reassessing the human immunodeficiency virus type 1 life cycle through age-structured modeling: life span of infected cells, viral generation time, and basic reproductive number, R0. J Virol. 2009; 83:7659-7667.

Curriculum vitae

Anneke Susanne de Vos was born on the 1st day of February of 1983, in Amsterdam, the Netherlands. She graduated at the Pieter Nieuwland College in Amsterdam in 2001, starting a study in biology that same year at the University of Amsterdam. In 2008 she obtained her Masters degree in Biological Sciences, having chosen the Track Ecology and Evolution, with a specialisation in Evolutionary and Ecological Dynamics.

During this specialisation she mathematically modelled the effect that a marine reserve would have on an age-structured fish population. For a second research project she modelled an age-structured HIV-infected cell population, to study within-host viral dynamics, at the University of Utrecht. She also wrote a literature based thesis entitled "Choosing kindness, is human altruism selected for by mate choice?".

In 2009 she obtained a position as a PhD student at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, in Utrecht. Here she studied, also in collaboration with the GGD (Public Health Service) of Amsterdam, the spread of blood-born infection among injecting drug users. In these mathematical modelling studies, she did not neglect that heterogeneity in risk-behaviour matters. The results of said research are presented in this thesis.