**Model Description**

A deterministic mathematical model was developed to simulate the transmission of HIV and HCV amongst PWID. The model incorporates the transmission of HIV and HCV due to injecting drug use as well as HIV transmission due to sexual risk behaviour. The total PWID population (population size) is divided into ten classes depending on the HIV and HCV infection status of the individuals, with these classes stratified by whether the PWID has low or high injecting risk. The total population of the low risk group is  and that of the high risk group is . PWIDs transition from high to low risk behaviour at a rate and from low to high risk at a rate . New PWIDs enter the model population at a rate and leave all compartments due to non-HIV death at a rate , or ceasing injection at a rate . The inflow rate is such that it balances non HIV deaths and cessation ( with all new entrants being susceptible to infection and a proportion (the initial proportion ) being high risk and the rest low risk.

The ten HIV and HCV infection classes included in the model are denoted by two letters: a capital letter representing the five HIV infection state ( for susceptible HIV, for acute phase of HIV, for latent phase of HIV, for ART and for lost to follow-up from ART and infected with HIV) followed by a lower case letter representing the two HCV infection state (for susceptible HCV and for chronic HCV). HCV treatment is not included in the model because treatment rates were low over this period [1](#_ENREF_1). The classes are denoted as follows: those that are susceptible to both HIV and HCV, susceptible to HIV but chronically infected with HCV, acute infection with HIV and susceptible to HCV , acute infection with HIV and chronic HCV , latent infected with HIV and susceptible to HCV , co-infected with latent HIV and chronic HCV , HIV on ART and susceptible to HCV , HIV on ART with chronic HCV , lost to follow-up from ART and susceptible to HCV , and lost to follow-up from ART with chronic HCV . A subscript is used to denote the low and high risk groups with  for low risk PWID and =2 for high risk PWID.

The model simulates the transmission of HIV and HCV, with the rate at which susceptible PWID become infected with HIV (force of infection ) or HCV (force of infection ) being proportion to the prevalence of HIV and HCV, respectively, which can both change over time through the effect of interventions and other factors. Those who become HIV infected enter the high viraemia acute phase of average duration and then progress to a lower viraemia latent stage. HIV transmission is elevated during the acute stage of HIV (by a factor α1)[2](#_ENREF_2). Individuals who are in the HIV latent state are recruited on to ART at a rate ω(t) and experience HIV related death at a rate . The HIV related death rate is reduced by a factor λ for PWID on ART while parenteral and sexual HIV infectivity are reduced by a relative amount and , respectively, compared to the HIV latent phase. A proportion of those on ART are lost to follow-up at a rate per year. Individuals who are lost to follow-up experience HIV-related death at the same rate as individuals in the HIV latent state () and are assumed to not be recruited back on to ART as suggested by data from Vancouver [3](#_ENREF_3). For HCV transmission, a proportion of those who are HCV infected spontaneously clear the acute infection to become susceptible again while the remaining proportion progress to chronic infection. The acute phase of HCV was not modelled explicitly because previous modelling analyses have shown this simplification has little effect on the patterns of HCV transmission[4](#_ENREF_4),[5](#_ENREF_5). Chronically HCV infected individuals are assumed to remain in the infected class until death or cessation. The factor denotes the decrease in the proportion of individuals that spontaneously clear HCV infection if they are HIV infected, while is the factor increase in HCV infectivity amongst individuals that are co-infected with HIV and HCV.

The schematic for the HIV and HCV classes of the model is shown in Figure 2 (in the main paper) and the model is defined by the following differential equations.

1. PWID susceptible to HIV
2. PWID in acute HIV stage

1. PWID in the HIV latent stage

1. PWID infected with HIV and on ART

5. PWID lost to follow-up infected with HIV

The model assumes that there is a probability  that any PWID in risk group  has a transmission contact with an PWID in risk group such that if and only if and zero otherwise, we have

 and ,

where is the degree to which PWIDs in either risk group mix assortatively (like-with-like mixing) or otherwise proportionately (depending on the relative total number of transmission contacts provided by PWID in each risk group), with probability . It is important to note that this formulation allows for flexibility to either assume like-with-like mixing () or proportionate ‘random’ mixing (). The parameter is the factor increase in injecting transmission risk for high risk PWID compared to low risk PWID. Through stratifying PWID by low and high risk, we allow for HCV-infected PWID to have a higher rate of HIV transmission, as suggested by data and recent modelling[6](#_ENREF_6),[7](#_ENREF_7), because higher risk PWID will have a higher rate of both HCV and HIV acquisition. Otherwise, we do not assume that HCV infected PWID have greater susceptibility to HIV infection. The transmission rates for HIV for low and high risk PWID are given by:

,

,

where τ is the proportion of the baseline HIV transmission rate that is due to sexual HIV transmission which is not affected by changes in injecting risk γ(t) but is affected by ART (. The transmission rates for HCV are given by

,

,

and

where is the HIV transmission rate in the latent stage of HIV and is the factor difference in the HCV transmission rate compared to this HIV transmission rate. The model does not explicitly incorporate risk behaviours such as the frequency of sharing syringe or injecting paraphernalia; instead this is implicitly incorporated within the HIV transmission rate . The model allows for decreases in injecting risk over the period 1996 to 2007, due to increases in intervention coverage or decreases in other factors related to heightened transmission risk. This is modelled through allowing for a relative decrease in the overall injecting transmission risk over time denoted by , with denoting the baseline level of injecting risk (in 1996) and that injecting risk has not changed over the period 1996 to 2007, and denoting the maximum reduction in injecting risk - a 100% reduction in injecting risk over that 10 year period compared to baseline levels in 1996.

**Non-inclusion of HCV related death**

For HCV mono-infection, HCV causes excess death, but this generally occurs over a long period of time. A meta-analysis from 2008 [8](#_ENREF_8) showed that after 20 years of infection, the estimated prevalence of cirrhosis will be 7% (4-12%) amongst mono-infected individuals in a non-clinical setting. This was confirmed for PWID by a more recent meta-analysis, which found the average time to cirrhosis from HCV infection for mono-infected PWID was 34-46 years [9](#_ENREF_9). Modelling has also shown that HCV mono-infection would only change the life expectancy of individuals at 25 years old from 43 years to 39.5 years [10](#_ENREF_10), and this is without including the excess mortality related to drug use [11](#_ENREF_11).

For PWID with HCV-HIV co-infection, but not on ART, evidence suggests that HIV increases the progression of HCV chronic infection to cirrhosis 2.5-times compared to those with HCV mono-infection [12](#_ENREF_12), and increases the death rate from decompensated cirrhosis 2.3-fold [13](#_ENREF_13). However, without ART, HIV mortality will be the dominant reason for death, with modelling undertaken by the authors suggesting that HCV co-infection would only change the average life expectancy of a HIV infected individual (without ART) from 9.8 to 9.7 years [10](#_ENREF_10).

For PWID with HCV-HIV co-infection and on ART, evidence suggests that ART reduces the HIV induced elevated rate of HCV progression from chronic to cirrhosis by 33%[12](#_ENREF_12). Modelling suggests the effect of this on life expectancy for a HIV infected individual on ART will be small with the life expectancy of someone with HIV-HCV co-infection and on ART being 22.7 years compared to 24.5 years for someone with HIV mono-infection [10](#_ENREF_10).

Therefore, it is likely that the HCV related death rate amongst HCV mono-infected PWID and co-infected PWID on or off ART is likely to be small compared to other competing death rates and the rate of injecting cessation. This is borne out in mortality data from the VIDUS and ACCESS cohorts which recently found that the rate of death due to liver disease amongst their PWID cohort was only 2.1 per 1000 person years overall, and contributed only 6.0% of deaths amongst anti-HCV positive PWID[14](#_ENREF_14),[15](#_ENREF_15). For this reason, HCV related death was not incorporated into the model.

**More detailed model parameterisation section**

All transmission and natural history parameters were obtained from the literature and can be found in Table 1 in the main text of the paper. Uniform uncertainty bounds were assigned to all model parameters. The only exceptions were: 1. The HIV transmission rate during the latent stage of HIV () and the factor difference between the HIV (during latent stage of HIV) and HCV transmission probabilities () which were varied freely to fit the model to the HIV and HCV prevalence amongst PWID in Vancouver at baseline[16](#_ENREF_16); and 2. The efficacy of ART in reducing an PWID’s parenteral HIV infectivity (), and the factor decrease in HIV and HCV transmission risk due to decreases in injecting risk (), which were varied to consider the impact of different intervention combinations. More details on how this was done is given in the next section. Coinciding with the increase in OST coverage from 1996 to 2002 and decrease in recent incarceration over the same period[17](#_ENREF_17), injecting risk was assumed to decrease linearly over 1996 to 2002 and then remain stable at its chosen value after that. The effectiveness of ART at reducing HIV transmissibility ( amongst HIV infected PWID was allowed to vary widely due to both the lack of data on the efficacy of ART in reducing injecting HIV transmission, and recent data suggesting that the efficacy of ART could be less in real life settings [18](#_ENREF_18),[19](#_ENREF_19) than was found in recent trials and observational studies[20](#_ENREF_20),[21](#_ENREF_21).

The death rate for PWID in Vancouver was estimated to be 3% per year in the VIDUS cohort [17](#_ENREF_17). However, because this included HIV mortality, a lower non-HIV death rate (rate ) of 1.5-2.0% per year was applied in the model coinciding with the death rate of HCV antibody positive individuals in the Vancouver Chase cohort[22](#_ENREF_22). The duration of HIV until death was assumed to be 10 years (rate =1/10) without ART[23](#_ENREF_23),[24](#_ENREF_24). HIV survival was assumed to be extended four-fold if on ART (factor =1/4)[25](#_ENREF_25) based on mortality data from PWID for 1996 to 2007 coinciding with our study period, but was varied between 2 and 6-fold to allow for uncertainty and the effect of discontinuation of treatment.

To be conservative, ART was assumed to decrease sexual HIV transmission () by 50 to 90% [20](#_ENREF_20) with the lower bound based on the proportion of PWIDs on ART that were virally suppressed 12 months after ART initiation in Vancouver at this time[26](#_ENREF_26). The rate of recruitment on to ART () was calibrated such that the proportion of HIV infected PWID on effective ART (HAART) was negligible in 1996 [27](#_ENREF_27),[28](#_ENREF_28), but then increased up to 40% by early 2000, after which it remained stable until 2006[28](#_ENREF_28),[29](#_ENREF_29). Any uncertainty in this coverage estimate was assumed to be accounted for in the uncertainty surrounding the effect of ART on extending HIV survival and reducing HIV infectivity. We assumed a rate of loss to follow up () from ART based on data from a recent study[3](#_ENREF_3) that found that individuals in Vancouver frequently cycle on and off ART, with the mean duration on ART being 17 months and the mean duration off ART being 6.5 months, but with 12% of those that discontinue ART never returning to ART during follow up. This study also found that the rate of being lost to follow up from ART was 1.98-fold higher if the individual was a PWID and decreased over calendar year compared to 1996-1999 by 10% for 2000-2003 and 14% for 2004-2007. We only modelled the permanent loss to follow up from ART, while assuming that any short periods of ART discontinuation would be accounted for in a lower real-life efficacy of ART for reducing HIV morbidity and HIV infectivity. We estimated the rate of permanent loss to follow up by firstly estimating the rate of any loss to follow up from ART as 70.6% per year (inverse of mean duration on ART in years). Then we scaled that up 1.98-fold to give an estimate for the loss to follow up rate for PWID, scaled that down by 10% to estimate the rate of loss to follow up for the middle time period we are considering (2000-2003), and then assumed that 12% of these are permanently lost to follow up from ART. This gave a permanent loss to follow up rate of 15.1% (0.706\*1.98\*0.9\*0.12=0.1509) which we allowed to vary between plus and minus 30% of this value because of uncertainty in this estimate and to see how it affected our projections.

Unbiased estimates of the average duration of injecting until permanent cessation are unavailable for Vancouver, so an average injecting duration of 11 years was assumed based on the median injecting duration reported in the VIDUS cohort [30](#_ENREF_30), but varied between 7 and 23 years because of the uncertainty in these estimates as discussed in a previous analysis by the authors [4](#_ENREF_4).

Because of uncertainty in the reliability of syringe sharing data to directly model HIV and HCV transmission risk, due to unknown biases in the data [*31-35*](#_ENREF_31), uncertainty over the role of paraphernalia sharing[*36*](#_ENREF_36)*,*[*37*](#_ENREF_37), and massive uncertainty in the HIV and HCV transmission probabilities[*38*](#_ENREF_38)*,*[*39*](#_ENREF_39), we did not model transmission mechanistically by estimating the number of syringe sharing and paraphernalia sharing incidents. Instead, we fit baseline HIV and HCV transmission rates by fitting the model to baseline levels of HIV and HCV prevalence and incidence. In addition, the factor increase in transmission risk for high risk PWID compared to low risk PWID () was also not estimated mechanistically but was set to be between 1-4.8 based on the enhanced HIV or HCV transmission risk associated with daily cocaine/heroin injecting or unstable housing in the VIDUS cohort[16](#_ENREF_16),[40](#_ENREF_40), with 30-60% () of PWID being assumed to be high-risk, similar to the proportion in unstable housing or crack/heroin injecting in 1996[17](#_ENREF_17).

To incorporate the importance of sexual HIV transmission in to the model, a literature review was first undertaken to identify HIV incidence studies from VIDUS (more details of the search and review are discussed later in the supplementary material) that considered whether sexual risk factors were important determinants of HIV sero-conversion. In general, studies found that few sexual risk factors were important, or were only significant in univariate analyses, whereas numerous injecting risk factors were strongly predictive of HIV sero-conversion. The only possible sexual risk factor consistently associated with HIV sero-conversion, as found in a number of multivariate analyses, is reporting ‘having a HIV-positive sexual partner’[41-43](#_ENREF_41). After adjustment for other risk factors, Kerr et al. found this behaviour elevated the risk of HIV acquisition 2.4 (1.3-4.6) times[41](#_ENREF_41). At baseline, 4.8% (49/1013) of PWID recruited into the VIDUS cohort (with at least one follow up) reported ‘having a HIV-positive sexual partner’, and in all follow up visits between May 1996 and May 2003 (PWID had a median of 8 follow up visits), the behaviour was reported in approximately 4.8% (391/(8\*1013)) of visits[41](#_ENREF_41).

By estimating the population attributable fraction (PAF), data from Kerr et al.[41](#_ENREF_41) suggests this risk factor accounts for 6.4% (1.0-18.5%) of HIV sero-conversions in VIDUS between 1996 and 2003. Although it is uncertain whether this risk wholly relates to sexual HIV transmission, this PAF estimate was used to give a possible estimate for the importance of sexual HIV transmission amongst PWID in VIDUS. However, because other unobserved sexual risk factors may have been important for HIV transmission in this setting, and to ensure we don’t underestimate the importance of sexual HIV transmission, an expanded range was incorporated into the model: It was assumed that 10% (5-25%) of the baseline HIV incidence was due to sexual HIV transmission and so could not be affected by reductions in injecting risk but could be reduced by increases in ART usage.

Other sexual risk factors that were not found to be related to HIV sero-conversion amongst PWID in VIDUS (not significant at p<0.05 in adjusted multivariate analyses) included having sex with another man[42](#_ENREF_42), being involved in the sex trade [41](#_ENREF_41),[42](#_ENREF_42),[44-49](#_ENREF_44), having over 20 sexual partners in lifetime [49](#_ENREF_49),[50](#_ENREF_50), and condom use or unprotected/unsafe sex [40-49](#_ENREF_40),[51](#_ENREF_51),[52](#_ENREF_52).

The baseline (1996) HIV and HCV prevalence and incidence estimates for the model came from the VIDUS cohort. The HCV and HIV antibody prevalence came from PWID recruited into VIDUS between 1996 and 1999, giving 82% and 21% [16](#_ENREF_16), respectively. However, because on average 26% of individuals spontaneously clear acute HCV infection [53](#_ENREF_53), a baseline HCV chronic prevalence of 61% was assumed. The 95% confidence intervals around these estimates were used in the model fitting. Data on the HCV and HIV incidence amongst PWID for Vancouver was extracted from Drug situation in Vancouver report (2009)[17](#_ENREF_17) and Wood et al., (2009)[40](#_ENREF_40), respectively. Because of uncertainty and fluctuations in the HIV and HCV incidence estimates and trends, negative exponential curves (with non-zero HIV or HCV incidence asymptotes) were fit to the incidence data from 1996 to 2007 by using the nonlinear least squares method in R which also produced 95% confidence intervals (95% CI) around the trends. This suggested that HIV and HCV incidence decreased by 84% (95% CI 76-86%) and 80% (95% CI 76-89%), respectively, over the decade. The curve fits are shown in Figure 3.

**Model calibration to baseline data**

The uncertainty bounds of the baseline HIV and HCV prevalence and all model parameters in Table 1 were randomly sampled 5000 times, except for the HIV transmission rate during the latent stage of HIV (), factor difference between the HIV and HCV transmission probabilities (), efficacy of ART in reducing an PWID’s HIV infectivity (α2), recruitment rate on to ART ((t)), and relative decrease in HIV and HCV transmission risk due to decreases in injecting risk (). For the initial fitting, the efficacy of ART (α2), recruitment rate onto ART () and the relative decrease in injecting risk ((t)) were set to 0, so that they had no effect on transmission in 1996. The reasons for the ART assumptions are discussed in the model parameterisation section. In contrast, we assumed the injecting risk in 1996 was a baseline upon which any reductions in risk would be incremental, i.e. means there was no change in HIV or HCV infection risk since 1996 whereas means injecting risk reduced to nothing from 1996 to 2007.

For each of the sampled parameter sets, the HIV transmission rate () and factor difference between the HIV and HCV transmission probabilities () were varied to fit the model’s projected endemic HIV and HCV prevalence to the sampled baseline HIV and HCV prevalence amongst PWID in 1996. The model’s predicted HIV and HCV incidence for each of these runs was then compared to the estimated HIV and HCV incidence from the curve fits for 1996, and any model run that lay within the 95% confidence bounds of the curve fit estimates were retained as a *baseline model fit* (2040 *baseline model fits*) while all others were rejected (2960 runs).

The ART recruitment rate () was then adjusted so that the coverage of ART amongst HIV+ PWID increases up to 40% by early 2000s, while assuming ART reduces HIV mortality, and then remains stable after this point [28](#_ENREF_28) for all model runs. The function which defines is given by

where and are both fit to achieve the required coverage of ART described above.

**Model calibration to incidence trend data and subsequent model analyses**

The model was then used to estimate the likely contribution that ART or changes in injecting risk made to the observed reduction in HIV and HCV incidence amongst PWID in Vancouver between 1996 and 2007. For each baseline model fit, an estimated final HIV and HCV incidence in 2007 was randomly sampled from the 95% confidence bounds of the curve fitted incidence estimates for 2007. For each sampled HIV and HCV incidence estimate, the baseline model fits were used to determine what combinations of ART efficacy for reducing injection-related HIV infectivity () and decreases in injecting risk () could result in the associated decreases in HIV and HCV incidence over ten years. The function defining was given the following negative exponential form because evidence from Vancouver suggests that injecting risk decreased gradually over this period, as suggested by data on decreases in syringe sharing [17](#_ENREF_17),[52](#_ENREF_52) and increases in OST coverage [17](#_ENREF_17).

where is the end resulting decrease in injecting risk, and is the rate at which injecting risk decreases, with both parameters being fit to give the decrease in HCV incidence over time. The parameter ensures that decreases in injecting risk are zero in 1996 and the bounds set on this variable ensures it cannot be larger than 1.

Fitting of and was done concurrently for all parameters by using the Matlab function lsqnonlin which uses the trust region reflective numerical algorithm to minimise the squared error between the model and decrease in HIV and HCV incidence. However, runs were rejected if the decrease in injecting risk needed to achieve the sampled decrease in HCV incidence resulted in a decrease in HIV incidence larger than observed. The solutions were then checked to see if the error between the model and observed incidence in 2007 was less than 0.001 per 100 person years. This produced 902 *full model fits*.

The new *full model fits* were then used to estimate what proportion of the modelled decrease in HIV incidence would have occurred with just the effect of ART included (decrease in injecting risk () set to zero over time), without the effect of ART included (ART efficacy for reducing injection-related and sexual HIV infectivity ( and ) set to zero), and with neither intervention included, and 2.5% to 97.5% percentile uncertainty bounds were produced around these estimates by using the projections across all model fits. This was used to estimate the degree to which ART contributed to the observed decrease in HIV incidence in Vancouver. An ANCOVA analysis was then undertaken to determine which model parameter and inputs contributed most to the uncertainty in our projections of the importance of ART.

**Literature review on the importance of sexual and injecting risk factors for HIV transmission amongst PWID in Vancouver**

To assess whether there were any sexual risk behaviours that could be linked to HIV incidence among PWID in Vancouver, studies investigating sexual (and non-sexual) risk factors for HIV among PWID in Vancouver were identified by searching on PubMed. Keywords in the database search included (IDU or PWID or "injecting drug user" or "injecting drug users" or "injection drug user" or "injection drug users" or "people who inject drugs" or "intravenous drug user" or "intravenous drug users") and (HIV or HIV-1) and Vancouver and  (incidence or seroconversion or vidus or prospective or longitudinal)

Of the 215 references retrieved by using the above mentioned key words, 16 articles were found to be relevant and factors associated with HIV incidence from these articles and period of surveys were noted. Where possible, the population attributable risk fractions due to any of the risk factors were obtained. Results from the Vancouver PWID surveys show that in earlier surveys, condom use amongst regular partners was frequently reported to be low between 1996 and 2000 (<21% for regular sex partners and <24% for casual sex partners) [42](#_ENREF_42),[44](#_ENREF_44), and was also low in a later survey from the safe injecting site in 2003 (30% amongst regular partners and 13% amongst casual partners)[54](#_ENREF_54), suggesting that sexual risks had not reduced appreciably during the rapid decline in HIV incidence amongst VIDUS PWIDs in Vancouver.

In terms of factors related to HIV sero-conversion, studies found that few sexual risk factors were important, with only reporting having a HIV-positive sexual partner generally being associated with HIV sero-conversion in a number of multivariate analyses[41-43](#_ENREF_41). It is uncertain whether this relates to sexual or parenteral HIV transmission. Although Kerr et al., (2006)[41](#_ENREF_41) pointed out that having an HIV positive partner is not sufficient evidence for sexual HIV transmission among IDUs, they suggested that sexual risks likely played a role because having an HIV positive partner remained a risk factor even after extensive adjustment for other risk factors including frequent heroin and cocaine injection and syringe sharing with sex partner. Other sexual risk factors were sometimes significant in univariate analyses, such as sex with another man[42](#_ENREF_42), being involved in sex trade [41](#_ENREF_41),[42](#_ENREF_42),[44-47](#_ENREF_44),[49](#_ENREF_49),[55](#_ENREF_55), and having over 20 sexual partners in lifetime [49](#_ENREF_49),[50](#_ENREF_50), but none of these were significant in the multivariate analyses. Other sexual risk factors were never related to sero-conversion, either in the univariate or multivariate analyses, including such things as condom use or unprotected/unsafe sex[40-47](#_ENREF_40),[49](#_ENREF_49),[51](#_ENREF_51),[52](#_ENREF_52),[55](#_ENREF_55).

In contrast, a number of injecting related risk factors were generally always related to HIV sero-conversion in multivariate analyses, such as daily or frequent injecting of cocaine[40-47](#_ENREF_40),[50-52](#_ENREF_50),[55](#_ENREF_55),[56](#_ENREF_56) or speedball[44](#_ENREF_44), requiring help injecting[41-43](#_ENREF_41),[45](#_ENREF_45),[47](#_ENREF_47),[56](#_ENREF_56), binge drug use [41](#_ENREF_41),[44](#_ENREF_44),[47](#_ENREF_47),[55](#_ENREF_55), and borrowing needles[42](#_ENREF_42),[46](#_ENREF_46),[51](#_ENREF_51),[55](#_ENREF_55),[56](#_ENREF_56), suggesting that injection-related HIV transmission dominated in the late 90s and early 2000s.

**Supplementary Figure 1:** ANCOVA projections of the percentage of the variation in the model’s projected contribution of ART to decreasing HIV incidence in Vancouver accounted for by different model parameters or inputs**.**



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