Drug and Alcohol Dependence 123 (2012) 122–131

Contents lists available at SciVerse ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Understanding the trends in HIV and hepatitis C prevalence amongst injecting drug users in different settings—Implications for intervention impact☆

Peter Vickerman[a,b,*], Natasha K. Martin[b,a], Matthew Hickman[b]

[a] London School of Hygiene and Tropical Medicine, London, UK
[b] University of Bristol, Bristol, UK

ARTICLE INFO

Article history:
Received 31 August 2011
Received in revised form 11 October 2011
Accepted 30 October 2011
Available online 3 December 2011

Keywords:
HIV
HCV
Injection drug users
Intravenous drug users
Substance abuse
Modelling

ABSTRACT

Background: A recent systematic review observed that HIV prevalence amongst injectors is negligible (<1%) below a threshold HCV prevalence of 30%, but thereafter increases with HCV prevalence. We explore whether a model can reproduce these trends, what determines different epidemiological profiles and how this affects intervention impact.
Methods: An HIV/HCV transmission model was developed. Univariate sensitivity analyses determined whether the model projected a HCV prevalence threshold below which HIV is negligible, and how different behavioural and epidemiological factors affect the threshold. Multivariate uncertainty analyses considered whether the model could reproduce the observed breadth of HIV/HCV epidemics, how specific behavioural patterns produce different epidemic profiles, and how this affects an intervention's impact (reduces injecting risk by 30%).
Results: The model projected a HCV prevalence threshold, which varied depending on the heterogeneity in risk, mixing, and injecting duration in a setting. Multivariate uncertainty analyses showed the model could produce the same range of observed HIV/HCV epidemics. Variability in injecting transmission risk, degree of heterogeneity and injecting duration mainly determined different epidemic profiles. The intervention resulted in 50%/28% reduction in HIV incidence/prevalence and 37%/10% reduction in HCV incidence/prevalence over five years. For either infection, greater impact occurred in settings with lower prevalence of that infection and higher prevalence of the other infection.
Discussion: There are threshold levels of HCV prevalence below which HIV risk is negligible but these thresholds are likely to vary by setting. A setting's HIV and HCV prevalence may give insights into IDU risk behaviour and intervention impact.

1. Introduction

Hepatitis C (HCV) and HIV are easily transmitted through contaminated syringes (De Carli et al., 2003; Baggaley et al., 2006). Although considerable variability exists in the HIV and HCV prevalence in different injecting drug user (IDU) populations, a recent systematic review reported a strong positive relationship between HIV and HCV prevalence in different IDU populations and observed very low HIV prevalences if HCV prevalence was less than 30% (Vickerman et al., 2009a). It was hypothesized that HCV prevalence could be a marker of the injection related HIV-risk for an IDU population (such that if HCV prevalence is below 30% then risk behaviour is too low to sustain HIV transmission). However, above this threshold, uncertainty exists on the reasons why IDU populations with similar HIV prevalence can have widely different HCV prevalences. For instance, an IDU population with 25% HIV prevalence can have a HCV prevalence ranging from 50% up to 90% (Vickerman et al., 2009a), suggesting that different risk behaviour profiles may result in similar HIV epidemics but widely different HCV epidemics.

The primary aim of this analysis was to assess whether a model of HIV and HCV transmission could reproduce several key findings from the systematic review. Firstly, the model was used to explore whether it could simulate the HCV prevalence threshold observed in the review data, and how univariate changes in different HCV transmission and natural history factors and IDU behavioural attributes affected the threshold. Secondly, a multivariate uncertainty analysis determined whether the model could reproduce the same broad spectrum of HIV and HCV epidemics observed in the review (Vickerman et al., 2009a), exploring how different behavioural patterns result in different HIV and HCV epidemic profiles and how these differences could affect the impact of interventions that reduce injecting transmission risk.

☆ Supplementary materials for this article can be found by accessing the online version of this paper at http://dx.doi.org. Please see Appendix A for more information.

* Corresponding author at: London School of Hygiene and Tropical Medicine, 15-17 Tavistock Place, London, UK. Tel.: +44 0 78211 96359.
E-mail address: peter.vickerman@lshtm.ac.uk (P. Vickerman).

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doi:10.1016/j.drugalcdep.2011.10.032

2. Methods

2.1. Model description

A previously published deterministic model of HCV and HIV transmission amongst IDUs was adapted for this analysis(Vickerman et al., 2009b). The model includes two subgroups of IDUs (denoted by a subscript i) with low ($i=1$) or high ($i=2$) transmission risk which mix either randomly (proportional to the overall transmission risk of each risk group) or partially assortatively (by ε% of IDUs) to form contacts that can result in HIV/HCV transmission. High-risk IDUs can transition to the low-risk state (rate ν) and are replaced by low-risk IDUs transitioning to the high-risk state (rate $\nu N_2/N_1$ where N_1 and N_2 are the number of IDUs in risk groups 1 and 2). IDUs leave the model if they cease injecting (rate μ), die (rate η) or experience severe HIV-related morbidity (rate Δ), and are replaced by IDUs entering the susceptible state for each risk group (rate Φ_i).

The model defines a monthly probability that an IDU will have an effective injecting HIV/HCV transmission contact (defined as monthly transmission probability). This transmission probability is increased (factor m) if an IDU is high-risk. An IDU's force of infection (Π_i for HIV and π_i for HCV) is dependent on the monthly transmission probability for that infection, the degree of assortative mixing between low and high-risk IDUs, the number of effective contacts supplied by low and high-risk IDUs, and their HIV/HCV prevalence.

The HIV transmission model assumes that once IDUs are infected (monthly injecting transmission probability β during latent phase of HIV) they progress to a high viraemia phase of infection (average duration $1/\zeta$), followed by a longer latent stage of low viraemia (average duration $1/\gamma$), a short period of high viraemia pre-AIDS (average duration $1/\lambda$), then AIDS (average duration $1/\Delta$) and death. HIV transmission is elevated during the initial (factor α) and pre-AIDs (factor κ) stages of HIV. The model does not simulate sexual HIV transmission.

The HCV transmission model assumes that once infected with HCV (monthly HCV transmission probability is a factor Ω greater than HIV transmission probability during the latent phase of HIV, $\Omega\beta$), IDUs enter an acute phase of infection (average duration $1/\sigma_1$) either leading to spontaneous clearance (probability δ_1) or lifelong chronic infection (probability $1-\delta_1$). All IDUs that spontaneously clear HCV are susceptible to re-infection (Grebely et al., 2006; Aitken et al., 2008) but have a higher probability (δ_2) of resolving re-infections (Page et al., 2009; Osburn et al., 2010; Vickerman et al., in press) which are shorter duration (rate σ_2) than primary infections (Osburn et al., 2010). All infected IDUs become antibody positive once infected and remain so thereafter. All HCV and HIV prevalence estimates are antibody prevalences.

To produce different HIV/HCV epidemics, the HIV transmission probability in the latent phase of HIV (β) is varied. The HCV and HIV model components are then run in parallel after HCV has reached an endemic state (changing by <0.05% over one year) without any HIV transmission included. The model follows the HIV/HCV co-infection state of all IDUs and assumes the HCV transmission probability is heightened in HIV/HCV co-infected IDUs (factor θ; Daar et al., 2001; De Carli et al., 2003; Yazdanpanah et al., 2005; Polis et al., 2007) and the probability of spontaneous clearance is reduced (factor ω; Thomas et al., 2000; Daar et al., 2001).

Fig. 1 shows the model schematics for the HIV and HCV model components (model equations in Supplementary material).

2.2. Model parameterisation

Biological parameters were obtained from the literature (Vickerman et al., 2009b). Ranges were assigned to all HCV-related parameters but point values were used for HIV-related parameters because we were primarily concerned with how the transmission dynamics of HCV compares to HIV and how uncertainties in our knowledge about HCV may affect this.

All behavioural parameters were given wide ranges so as to produce a broad range of HIV/HCV epidemic profiles. For instance, the ranges assigned to the relative size of the high-risk group and its heightened transmission risk came from IDU cohort studies where 10–60% of IDUs reported crack/cocaine injecting, homelessness, police harassment, and/or syringe/equipment sharing, factors associated with a 2–10-fold increase in HIV/HCV incidence (Rezza et al., 1996; van Beek et al., 1998; Patrick et al., 2001; Miller et al., 2002; Maher et al., 2007; Ruan et al., 2007; van Den Berg et al., 2007b; Craine et al., 2009; Turner et al., 2011). Little data exists on the degree to which IDUs mix like-with-like (Friedman et al., 1999; Hope et al., 2011) and whether IDUs transition between risk states (Vickerman et al., submitted for publication), so wide ranges were assigned to each.

All parameters, except the transmission probabilities, were also assigned point values to obtain two 'baseline' model runs that were used in the univariate sensitivity analyses (Section 2.3). These two runs had the same biological parameters and duration of injecting, but either assumed no (baseline run 1) or some (baseline run 2) heterogeneity in risk behaviour. See Table 1 for parameter ranges and the point values used for both baseline runs.

The model projections were compared against weighted HIV and HCV prevalence data from 310 different IDU populations collated in a systematic review (Vickerman et al., 2009a).

2.3. Univariate sensitivity analysis

A univariate sensitivity analysis was undertaken to explore whether the model's projected relationship between the endemic prevalence of HIV and HCV exhibited a similar threshold to the systematic review, with HIV becoming non-negligible (baseline prevalence > 1%) only when HCV had passed a specific prevalence. Specific changes were made to different model parameters and the HIV transmission risk was varied to produce different epidemic profiles. Firstly, baseline run 1 (assumes no risk heterogeneity) was used to consider univariate changes in the: primary or re-infection clearance probability or duration; relative transmissibility of HCV compared to HIV; degree to which HIV co-infection increases HCV infectivity or decreases spontaneous clearance; and IDU cessation rate. Then baseline run 2 (assumes risk heterogeneity) was used to consider high-risk groups of different sizes and heightened risk that mix randomly or partly assortatively (like-with like), and remain high-risk for different durations.

Additionally, a univariate sensitivity analysis using baseline run 1 explored varying the duration of the HIV epidemic (10–40 years representing the likely range of IDU HIV epidemic durations, HCV at endemic state). Table 1 presents the range of parameter values used for each univariate sensitivity analysis; all other model parameters were kept fixed as for that baseline run. Wide ranges were considered for all behavioural and epidemiological parameter to explore whether the model would still simulate a similar relationship between HIV and HCV prevalence as in the meta-analysis.

2.4. Multivariate sensitivity analysis

A small number of 'biological' scenarios were assigned to the HCV transmission and natural history parameters based on whether they had a non-negligible effect in the univariate sensitivity analysis, with most biological parameters given point values. A multivariate uncertainty analysis was undertaken for each scenario, varying all behavioural and epidemiological parameters across the same values considered in the univariate sensitivity analyses (except for high-risk duration because it had little effect in the univariate analysis) with variable HIV epidemic durations (Table 1). Five hundred different parameter sets were randomly sampled to produce 500 HIV/HCV epidemics for each biological scenario. All parameter values were sampled uniformly, except for the HIV transmission probability which was preferentially sampled from its lower range to give a relatively even spread of HIV/HCV epidemic profiles.

For each biological scenario, the 500 end-point HIV/HCV prevalence projections were compared against data from the systematic review (Vickerman et al., 2009a) to evaluate whether the model gave the same range of HIV/HCV epidemics as observed in the data, and determine which HCV biological scenarios gave the best agreement with data.

2.5. Determinants of epidemic type and intervention impact

A resampled ($n=2000$ instead of 500) batch of model projections from a biological parameter scenario that agreed well with data were used to explore which behavioural and epidemiological factors were important for achieving different HIV/HCV prevalence combinations. Partial rank correlation coefficients (correlation coefficient $\beta \geq 0.2$) and grid plots were used to evaluate the importance of each factor.

The resampled model simulations were also used to project the impact of a generic intervention that resulted in a 30% reduction in HIV/HCV injecting transmission risk amongst all IDUs. This is in line with the likely impact of a large proportion (~60%) of IDUs being on high coverage needle provision, which has recently been shown to reduce HCV incidence by about 50% (Turner et al., 2011). The intervention was initiated after the HIV/HCV epidemics had reached their baseline HIV epidemic duration (10–40 years), and the relative decrease in HIV/HCV incidence and prevalence was assessed after five years. Grid plots and linear regression (impact measure as independent variable and HIV/HCV prevalence as dependent variables) were used to assess how the intervention's impact varies for epidemics with different HIV and HCV prevalence.

3. Results

3.1. Univariate sensitivity analysis

For univariate changes in different model parameters, Figs. 2 and 3 present the relationship between HIV and HCV prevalence (endemic, except for Fig. 3f, where the HIV epidemic duration is varied) as transmission risk is increased. Overall, the figures show that the model exhibits a threshold HCV prevalence below which HIV prevalence becomes negligible (<1%), but that the relationship between HIV and HCV is likely to vary depending on numerous factors.