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CONTROL OF AN HIV EPIDEMIC AMONG INJECTION DRUG USERS: SIMULATION MODELING ON COMPLEX NETWORKS

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ABSTRACT

HIV remains a serious public health problem in many marginalized communities. We develop a network model of the HIV epidemic affecting injection drug users and female sex workers in the Downtown Eastside neighborhood of Vancouver, Canada, calibrated using data from public health surveillance and cohort studies. Many HIV positive individuals are unaware of their status and strategies for testing are an important part of HIV response programs. Upon diagnosis, HIV patients enter a continuum of care, involving both engagement and retention in treatment. We explored potential epidemic control strategies through simulation: reduced syringe sharing during injection drug use, reduced time to diagnosis, reduced time to initiation of treatment

following diagnosis, and improved retention in treatment. We find that syringe sharing, HIV testing, and retention in treatment significantly impact HIV prevalence. Close connections between syringe sharing and sexual networks deserve attention as important avenues for rapid HIV transmission.

1 INTRODUCTION

Human immunodeficiency virus infection (HIV) continues to be a major health threat in low and middle-income countries worldwide and severely affects many marginalized communities in high-income countries. Multiple epidemic drivers and barriers limiting the effectiveness of interventions can create complex problems for epidemic control programs. This poses many challenges for developing models to analyze potential response strategies. We address these challenges in the context of the HIV epidemic in the Downtown Eastside (DTES) neighborhood of Vancouver, Canada by developing a detailed large-scale network model of the HIV epidemic among people who inject drugs and women involved in sex work in this community.

Vancouver's Downtown Eastside, which is one of the poorest urban neighborhoods in Canada, experienced an explosive outbreak of HIV infection in the mid 1990s, due to widespread sharing of syringes among people who inject drugs. In a community of approximately 16,000 individuals, it is estimated that there were around 4,700 injection drug users (Buxton 2005) and that between a third and over half of women who inject drugs were involved in sex work (Strathdee et al. 1997, Tyndall et al. 2002). The HIV epidemic peaked in 1996 at an estimated 18.6 new infections per 100 person-years (Strathdee et al. 1997). (This unit of disease incidence is defined to be the number ofnew infections in a group of 100 susceptible individuals per year.) Harm reduction measures were implemented and access to treatment improved to address the outbreak. A syringe exchange program was expanded and North America's first supervised injection facility (Insite) opened in 2003. Syringe sharing dropped from 40% to 5% over the following decade (Kerr et al. 2010), because of the complete elimination of syringe sharing within the supervised injection facility and ready access to sterile syringes outside of it.

Combination antiretroviral therapy (ART) was introduced in 1996 and treatment coverage increased steadily in the DTES thereafter. ART suppresses viral replication when taken consistently and this reduces symptoms of HIV infection. Low levels of circulating virus in the blood and bodily fluids drastically reduce the risk of HIV transmission (Cohen et al. 2011). This effect of ART on HIV transmission is the rationale for the Treatment as Prevention public health strategy, which has become a foundation of global HIV policy (Montaner et al. 2014). The robust public health response in the DTES significantly reduced new HIV infections and stabilized the epidemic (Montaner et al. 2014). However, addiction, poverty, homelessness, food insecurity, and related challenges continue to drive sex work and injection drug use in the DTES. The community remains vulnerable to HIV infection.

The goal of our analysis is to inform the improvement of the HIV control program in the DTES. We developed a detailed social network model of the community, which included people who inject drugs and female sex workers. Network modeling enabled us to consider the complex context and multitude of interacting factors that drive the epidemic and influence the effectiveness of interventions. Detailed data on the social network structure for the DTES were not available. However, the network structure was based on published results for injection drug user and sexual networks (Liljeros et al. 2001, Schneeberger et al. 2004, Dombrowski et al. 2013). The modeling process was informed by extensive consultations with clinicians, epidemiologists, ethnographers, and HIV service providers who work in close collaboration with communities represented in this study. They contributed expertise in a variety of social and structural determinants that shape HIV risk, prevention, and treatment. Surveillance data and data from cohort studies were provided by the British Columbia (BC) Centre for Excellence in HIV/AIDS, the BC Centre for Disease Control and Vancouver Coastal Health regional health authority, which oversee delivery of HIV services and surveillance in the DTES. We used network simulations of harm reduction interventions and expansion of ART coverage to determine the potential impact of these programs on the epidemic, measured as changes in equilibrium HIV prevalence.

2 MODEL DEVELOPMENT PROCESS

2.1 Injection Drug Use in Vancouver's Downtown Eastside

There was a confluence of many policy, social, and economic factors in Vancouver's Downtown Eastside neighborhood that resulted in it becoming "a vortex of drug-related harm", which led to to an explosion of HIV and hepatitis C infection (Wood and Kerr 2006). The DTES is a poor, inner-city neighborhood with a concentration of low-income accommodations that became a focal point in the city's drug market and sex trades. Injection drug use in the DTES typically involves stimulants and opioids. Stimulants such as cocaine, crack cocaine (or "crack"), and methamphetamine (or "crystal meth") are typically injected more frequently than opioids due to their shorter period of action, resulting in an increased risk for HIV transmission (Tyndall et al. 2003). The most commonly used opioids are heroin and diverted prescription opioids (e.g., Percocet, dilaudid, morphine, Tylenol 3 & 4, Oxycontin, fentanyl, methadone) (UHRI 2003).

We briefly mention here some factors that informed our understanding of HIV risk in the DTES. Intense periods of high frequency drug use—usually injection of stimulants such as cocaine—is called "bingeing" and is an important risk behavior associated with increased syringe sharing (Wood et al. 2002) and HIV transmission (Miller et al. 2006). Single-room-occupancy hotels (SROs) are one of the primary forms of accommodation available in the DTES to low-income drug users and are notable for their unsanitary conditions, overcrowding, and rampant drug use. "Running partners" represent significant social relations where two or more drug users have an arrangement to share drugs, use together, and to rely on each other for assistance in the drug scene. Running partners potentially engage in higher risk behaviors among themselves than with others. Women who use drugs are at higher risk for HIV infection for many reasons including being more likely to have experienced sexual abuse, engage in sex work, smoke crack daily, and need help injecting (Miller et al. 2002, Spittal et al. 2002, Shannon et al. 2007).

2.2 Developing the Model

A multidisciplinary team of mathematicians, ethnographers, epidemiologists, clinicians, physicists, and computer scientists with extensive expertise in simulation modeling, HIV, injection drug use, and sexual health collectively developed a conceptual framework for a network model through an iterative process of ongoing consultation and regular integration workshops (Vasarhelyi et al. 2011). To inform the process, key contexts of HIV-related risk in the DTES were identified through literature review, scientific and community expert consultations, and review of published and unpublished data from a number of other DTES and injection drug user studies conducted at the BC Centre for Excellence in HIV/AIDS.

Key assumptions of the conceptual model were tested in two focus groups held with current and former injection drug users from the DTES. Separate focus groups were held for men and women, because a review of the literature and discussion with other researchers had identified that the experience of risk in the DTES may be different by gender. Data was elicited through the presentation of vignettes followed by semi-structured facilitated discussions. Vignettes described realistic and relevant syringe sharing scenarios in a variety of key local contexts including bingeing, sex work, and running partners, as well as settings such as in prison, single-room-occupancy hotels, and the supervised injection facility.

Key results from the focus groups included: confirmation that syringe sharing was no longer generalized, but continues in situations where barriers to typical usage practice would arise; involvement in sex work had an important impact on a variety of risks for women; deeper insight into the social structure of injection drug users in prison settings; and that sexual transmission was an important factor to include. The finding that risk behavior is affected by risk environment (Rhodes 2002) as well as by interpersonal influences was key to balancing the various dynamics in the model and provided insight into how to better incorporate incarceration into the model.

Interactions between sex workers and injection drug users in the DTES with the general population in Vancouver was not incorporated into the model. Street-based sex work and drug sales do occur with the general population. However, we assume that they do not contribute significantly to HIV spread in

the DTES, because prevalence in the general population is much lower than in the DTES. Furthermore, syringe sharing between injection drug users in the DTES and members of the general population would be rare.

3 NETWORK MODEL

3.1 Disease Models on Networks

Complex networks or random graphs can be used to model the dynamics of diseases, which are spread by direct contact between socially intimate individuals. This is in contrast to compartmental disease models, which assume complete mixing of subpopulations and random interaction between individuals (Anderson and May 1991). The spread of HIV through sexual contact or sharing of syringes by injection drug users is an example of an epidemic in which it is expected that social network structure would play an important role in epidemic dynamics and control strategies.

A complex network consists of vertices connected by edges. For a review of complex networks see Albert and Barabási (2002), Newman (2003), or Newman (2010). The vertices in our model represent individuals and the edges represent social contacts along which HIV can be transmitted. These are either sexual contacts, sharing of syringes by injection drug users, or both behaviors taking place concurrently. The degree of a vertex is the number of edges which are connected to it. The degree distribution p_k is the probability that a randomly chosen vertex has degree k. A scale-free network (Barabási and Albert 1999) is a network with a degree distribution that satisfies a power-law, $p_k \propto k^{-\alpha}$, where $\alpha > 2$. Studies of both sexual networks and injection drug user networks have shown that these networks are approximately scale-free, with α between approximately 2.5 and 3.5 (Liljeros et al. 2001, Schneeberger et al. 2004, Dombrowski et al. 2013). In reality, the degree distribution of these networks is likely to be closer to a truncated power-law distribution.

The epidemic threshold of a disease model is the value of the disease transmission rate above which an initial index case in the population will result in an epidemic outbreak. Compartmental disease models based on systems of differential equations typically exhibit a nonzero epidemic threshold. This implies that vaccinating only a fraction of the population will achieve immunity of the population to an epidemic outbreak. This is termed herd immunity. Mathematically, this corresponds to local stability of the disease free equilibrium in the model. Strategies for prevention and control of epidemics are largely based on this concept.

It has been shown that for many disease models on scale-free networks, the epidemic threshold is zero. For example, the epidemic threshold for both the standard susceptible-infected-recovered (SIR) model and an SIR model with multiple infection stages is zero for $2 < \alpha \leq 3$ (Pastor-Satorras and Vespignani 2001, Meyers 2007, Lou and Ruggeri 2010). The epidemic threshold for the susceptible-infected-susceptible (SIS) model is zero for $\alpha > 2$ (Chatterjee and Durrett 2009). Although these results are for mathematical idealizations of the real world, they nonetheless indicate that controlling epidemics on social networks which are approximately scale-free may be challenging.

Our model utilizes three types of stochastic processes on the underlying complex network. The first are *contact processes* in which a "disease" is transmitted from one vertex to another by a stochastic process with a given probability per unit time. The disease in question may be either an infectious pathogen or a social influence whereby one individual influences another to change social behavior. The second type of process is a *self process* in which a vertex changes state stochastically without any influence from its nearest neighbors in the network. These state changes may be progression through disease stages, treatment stages, or death. The third type of process is a *mean field process* in which a vertex changes state according to the prevalence of another state in the network. These processes are used to model situations in which an individual experiences random mixing with a subpopulation in the model, for example while they are incarcerated in prison. For simplicity, we assume that all of these stochastic processes are Markovian.

3.2 The Vancouver Downtown Eastside Model

The underlying social network in the DTES network model is generated using the Barabási-Albert preferential attachment algorithm (Barabási and Albert 1999). The degree distribution of networks generated with this algorithm approaches a power-law with $\alpha = 3$, as the size of the network approaches infinity. This degree distribution is expected to be a good approximation to the degree distribution of the actual injection drug user network and sexual network in the DTES, because both of these types of networks exhibit a power law in the degree distribution, at least up to large degree. The power observed in injection drug user and sexual network data is typically close to three (Liljeros et al. 2001, Schneeberger et al. 2004, Dombrowski et al. 2013). Other aspects of the social network topology would not necessarily be captured well by the Barabási-Albert algorithm. However, the degree distribution is the most important determinant of the equilibrium states of a disease process on a complex network.

Our network model of the DTES contains a total of 108 vertex states. As shown in Figure 1, the state space can be written as a Cartesian product of four property sets. The first is the gender risk, which includes gender and also whether or not females are sex workers. There are no male sex workers in the model. The second property is HIV status, which indicates whether the individual is infected with HIV, the disease stage, and the treatment status of the patient. The third property is the injection drug user (IDU) status of the individual, which could be one of not being an IDU, or being a light or heavy IDU. Heavy IDU in the model represent injection drug users that frequently engage in bingeing, as described in Section 2. The fourth property describes whether the individual is currently incarcerated. This state space was arrived at after extensive consultation with experts and focus groups with current and former injection drug users to determine the most important contexts and factors influencing HIV transmission in the DTES.

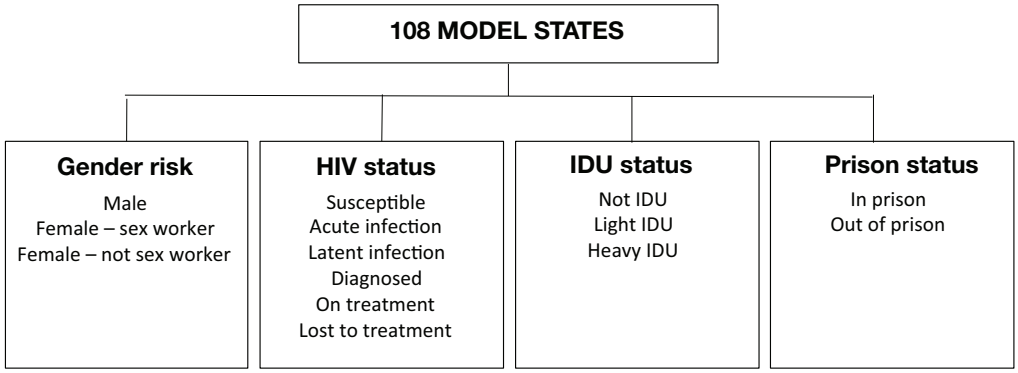


Figure 1: Vertex states of the DTES network model shown as the Cartesian product of four property sets. IDU denotes injection drug user.

Vertex state transitions in the model are implemented by one of a contact process, a self process, or a mean field process. These types of stochastic processes are described in Subsection 3.1. HIV transmission in the model is by a contact process between nearest neighbors in the network, unless the individual is in prison. HIV infection in prison occurs through mean field transmission with all other individuals in the model that are also in prison, which reflects the high degree of mixing that typically occurs between inmates. Progress through the acute and latent diseases stages of an HIV infection occurs through a self process. Likewise, diagnosis, treatment, and treatment interruption also occur through self processes. Individuals in the model change their IDU status under the social influence of their nearest neighbors in the network. This is modeled as a contact process. These state transitions are shown in a Unified Modeling Language (UML) state diagram in Figure 2. The parameters in the contact processes defined on the edges of the complex network depend on the states of the vertices at the ends of the edges. Therefore, the interactions between connected vertices vary dynamically, and in some instances may be temporarily turned off. A total of 176 parameters are required to define all state transition processes in the model.

Mortality is captured in the model by returning a vertex to a state with no risk or HIV status. The edges connected to the vertex are not changed when its state is reset. Although it may seem unrealistic for a reborn agent to retains its social connections, this has the advantage that it preserves the degree distribution of the network. Our analysis focuses on the equilibrium behavior of the model. In a more general model that allowed network edges to change dynamically, the equilibrium state of the model should still correspond to a steady-state degree distribution. Therefore, we decided to leave the network fixed after it was generated.

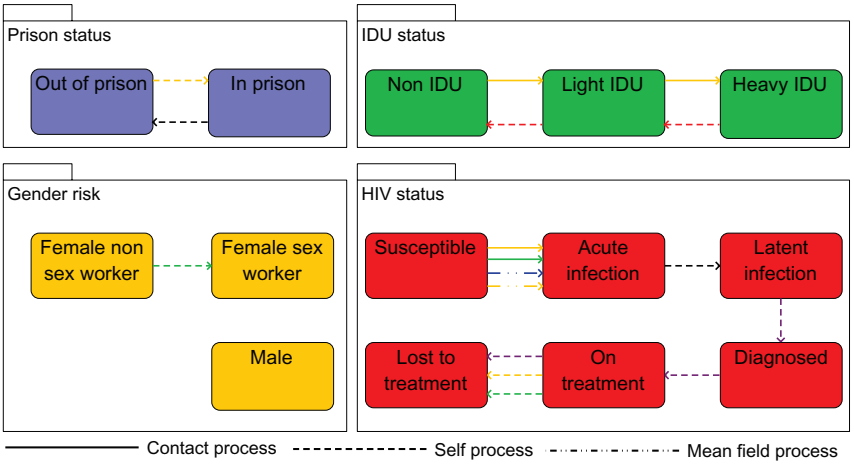


Figure 2: UML state diagram showing the transitions between vertex states. The type of transition process is shown by the type of arrow. The arrows are colored to show which other factor in the product state space influences the parameters in the stochastic process. Prison-related mean field transition from Susceptible to Acute infection in HIV status can only occur if the agent is in the In Prison state. All other transitions from Susceptible to Acute infection can only occur in the Out of prison state.

Model simulations are implemented using NepidemiX (Ahrenberg 2016), a python-based software suite developed by our group for modeling disease processes on networks. Vertex states and transition rules are specified in a configuration file, which NepidemiX uses to generate the simulation software code in python. The underlying network is generated using NetworkX (NetworkX 2016).

Each simulation run of the DTES network model begins by generating a Barabási-Albert network with 10,000 vertices. This network size is chosen because it provides a balance between good statistics for the stochastic simulation and reasonable run times for the simulations. This paper focuses on equilibrium analysis of the model, for which it is unnecessary that the number of vertices in the network match the population size. It is sufficient for the network to be large enough to approximate the large-size scaling limit of the model. All simulations of the epidemiological processes on the network are run until the model is close to stochastic equilibrium.

3.3 Calibration and Validation

The model was calibrated using HIV treatment data from the Drug Treatment Program at the BC Centre for Excellence in HIV/AIDS, epidemiological and social data from the Urban Health Research Institute (UHRI) in Vancouver, data from four cohort studies conducted in the DTES, population data from British Columbia Vital Statistics and Statistics Canada, public health surveillance data from the British Columbia Centre for Disease Control, and a survey of the literature. These data allowed us to calibrate 174 state transition parameters in the model. A description of how the data sources were used to calibrate the model is given in Table 1. A complete list of all model parameters with their values is too lengthy for inclusion here. The authors can provide further information upon request.

Data source	**Description of parameters calibrated**
BC Vital Statistics and Statistics Canada	all causes mortality
BC-CfE Drug Treatment Program	HIV/AIDS mortality, HIV diagnosis, HIV treatment initiation, HIV treatment interruption, HIV treatment in prison, HIV disease progression
BC Centre for Disease Control	HIV diagnosis
Urban Health Research Institute (UHRI)	IDU mortality, HIV status for IDU
ACCESS study (Milloy et al. 2012)	incarceration, HIV disease progression for IDU, HIV infection via syringe sharing, initiation of injection drug use
LISA study (Duncan et al. 2013)	IDU incarceration, HIV status in prison
MAKA study (Shannon et al. 2007)	sex worker mortality, sex worker incarceration, initiating sex work, cessation of sex work, initiation of sex work via injection drug use contacts, HIV infection rate for sex workers
VIDUS study (Hyshka et al. 2012)	incarceration, HIV disease progression for IDU, HIV infection rates via syringe sharing, initiation of injection drug use
Marks, Crepaz, and Janssen (2006)	risk behavior change after HIV diagnosis

Table 1: Cohort studies, treatment data, and public health surveillance data were used to calibrate 174 state transition parameters in the model. All parameters in the model are probability rates for Markovian processes.

The MAKA study was used to calibrate parameters in the model related to female sex workers. This study cohort included sex workers who self-identified as women, which also included transgender individuals. However, the women-identified sex worker population in the DTES is predominantly female and therefore, MAKA study data still provided sufficiently accurate estimates for parameters related to female sex workers.

Initiation of injection drug use and sharing of syringes spread on the social network in the model. This reflects the role played by social interactions in the drug scene. For simplicity, the model does not propagate drug use and syringe sharing behavior independently. Analysis of data from the VIDUS study was used to estimate that 3% of all drug injections involved syringe sharing and this percentage was treated as a constant in the model.

Two of the model parameters could not be obtained directly from data and these parameters were calculated by fitting the model to additional data. These are the probability rate for the contact process that models peer pressure in initiating injection drug use and the mean time to diagnosis after HIV infection. Analysis of surveillance data from the BC Centre for Excellence in HIV/AIDS for the HIV epidemic in the DTES showed that the epidemic was approximately at equilibrium—in other words, endemic— between 2010 and 2012. These two parameters were calculated by fitting the model results at equilibrium to five additional data values, which were not used in the model calibration in Table 1. HIV prevalence among injection drug users, female sex workers, and females who are not sex workers were used for model fitting. Also used were the prevalence of injection drug use in the community and HIV incidence among injection drug use. The fit computations were done using a parallelized two-dimensional grid search involving 1200 model runs on a computational cluster.

The results of model fitting are summarized in Table 2. The best model fit corresponds to a transmission probability or social influence rate for injection drug use behavior of approximately 0.7% per month and a mean time to diagnosis from acute stage HIV infection of approximately 50 months. In all cases, the model results agree with the findings from the cohort studies, within the expected accuracy of the data. This provides a good validation of the model, because there are three more data values than free parameters being fit. In other words, the model is over-determined.

	HIV prevalence			Prevalence of	Annual HIV
	IDU	**Sex worker**	**Not sex worker**	**injection drug use**	**incidence for IDU**
Cohort studies	27%	32%	21%	30%	2–3%
Model value	24%	33%	23%	34%	2.2%

Table 2: Model fitting results show comparisons of model output to data to estimate values for the two unknown parameters: the initiation rate of injection drug use under social influence and the mean time to diagnosis after the end of the acute HIV phase.

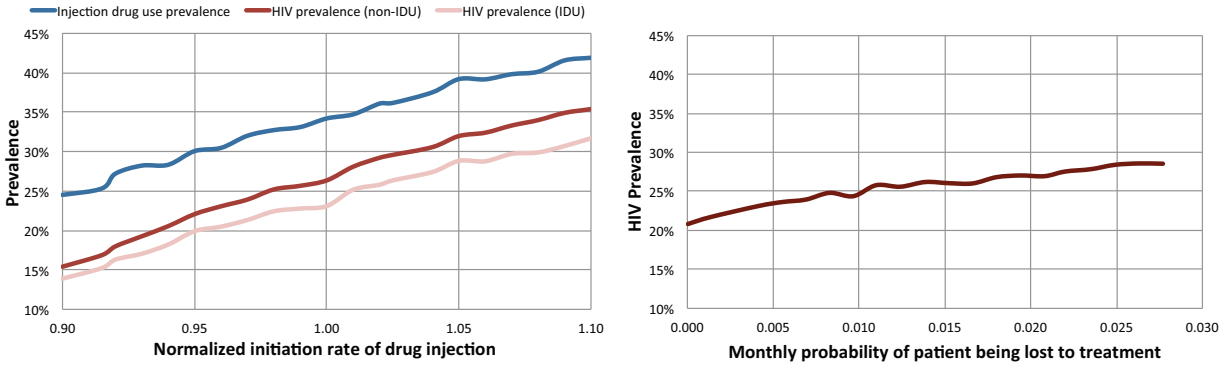
4 RESULTS

Model simulations were carried out to assess four potential strategies for addressing the HIV epidemic. These are a reduction in syringe sharing during injection drug use, a reduction in the time to diagnosis, a reduction in the time to initiation of treatment, and improvements to retention in treatment. The first of these scenarios represents harm reduction programs in the DTES and the remaining three represent components of the continuum of HIV care. The simulations used 26 time steps per year, or one time step every two weeks. This provided a good balance between sufficient temporal granularity for simulating the stochastic processes and acceptable computational performance. Equilibrium HIV prevalence is used as a measure of intervention effectiveness. Numerical analysis showed that for all parameter values studied, the model was sufficiently close to stochastic equilibrium after 8000 time steps. Each intervention strategy was analyzed at 20 different points in the parameter space, with the results for each point averaged over 20 independent model runs. For each simulation run, prevalence data was averaged over 500 time steps. The standard error in the simulation estimate of mean equilibrium prevalences using 20 independent runs was approximately 1% to 2%. This should not be interpreted as an estimate of model accuracy, because the data inputs to the model have measurement error. In nearly all cases, estimates of this measurement error is unavailable.

Figure 3 (a) shows the impact of changing the initiation rate of injection drug use through social network interaction on the prevalence of injection drug use, and the prevalence of HIV in both IDU and non-IDU individuals. These results can be interpreted more broadly as the effect of interventions which discourage the use of injection drugs, as well as harm reduction programs which provide sterile syringes or a supervised injection site. The model results show that injection drug use with syringe sharing can be a significant driver of HIV prevalence among both the IDU and non-IDU communities. HIV prevalence in the non IDU community is slightly higher than in the IDU community. This occurs because HIV-positive IDU have shorter life expectancy than HIV positive non-IDU. From the graph in Figure 3 (a), we see that a 10% reduction in the rate of initiation of injection drug use would reduce HIV prevalence in IDU from 24% to 14% and HIV prevalence in non-IDU from 26% to 15%.

Effective retention in treatment is critical to the success of the Treatment as Prevention strategy for controlling the HIV epidemic. The impact on HIV prevalence of changes in the probability of patients being lost to treatment is shown in Figure 3 (b). The probability rate of loss to treatment was approximately 1.4% per month in 2010, which is the year used for model calibration. Reducing treatment interruptions to negligible levels would reduce HIV prevalence from 26% to approximately 20%.

We also simulated a reduction in the time to diagnosis after acute stage HIV infection. This provides insight into the importance of testing strategies for HIV. We assumed that diagnosis cannot occur during the acute phase of HIV infection, because of the testing window period associated with HIV tests and challenges in identifying at-risk individuals for testing. If the mean time to diagnosis after the acute phase is shortened from its observed value of 50 months at calibration to two months, then HIV prevalence drops from 26% to 21%. An even greater reduction in prevalence would occur if a significant number of cases were diagnosed during the acute phase, because HIV positive individuals are more infectious during the acute phase (Bellan et al. 2015).



(a) (b)

Figure 3: (a) Equilibrium prevalence of injection drug use, and equilibrium prevalence of HIV among IDU and non-IDU as a function of the probability per month that an individual will become an injection drug user. The initiation rate for injection drug use influenced by social network interaction is normalized to a baseline value of one at model calibration. (b) Equilibrium prevalence of HIV in the entire model population as a function of the probability per month that a patient is lost to treatment. In 2010 when the model is calibrated, the monthly probability of being lost to treatment was approximately 0.014.

The final epidemic control strategy that we examined is earlier treatment initiation after diagnosis. We found that this strategy has the least scope for curtailing the epidemic. Changing the mean time to treatment initiation from 25 months at model calibration to zero reduces prevalence from 26% to 24%. The reduction in time to treatment in this scenario is not combined with a reduction in time to diagnosis. Therefore, the impact of earlier treatment is limited because diagnosis is a prerequisite for treatment.

5 DISCUSSION

We constructed a detailed network model of a marginalized inner-city community in Vancouver, Canada, and simulated strategies for controlling the HIV epidemic in this community. One strategy features a harm reduction intervention whereby injection drug use with syringe sharing is reduced and the others improve HIV testing and treatment delivery. HIV prevalence at equilibrium was used to evaluate the potential long-term influence of these interventions on the course of the epidemic. HIV prevalence was reduced by all control strategies considered and we discovered previously unknown aspects of the epidemic that are driven by the structure of social network connections in the neighborhood.

The modeling analysis demonstrated that syringe sharing by people who inject drugs would contribute significantly to the HIV epidemic in the entire Downtown Eastside neighborhood, and not only to HIV incidence among injection drug users. This is explained by the intimate partnerships and sex work linkages, which connect the syringe sharing and sexual transmission networks, creating highly efficient avenues for HIV transmission in this closely-knit community. Epidemiological studies have demonstrated the value of harm reduction programs that reduce syringe sharing in lowering risks of HIV transmission for people who inject drugs in the DTES (Reddon et al. 2011, Hyshka et al. 2012). Our model results reflect these findings and demonstrate that harm reduction programs which reduce syringe sharing would also effectively reduce new HIV infections in the wider Downtown Eastside community.

Improving HIV testing and treatment delivery lowers equilibrium HIV prevalence in the model. The three strategies studied are reducing time to diagnosis, time to treatment initiation, and likelihood of a patient being lost to treatment. Of these three strategies, the greatest impact on the HIV epidemic was realized through earlier diagnosis and better retention in treatment. These findings suggest that Treatment as Prevention could most effectively stem the epidemic, if a robust testing program and efficient services

for retaining patients in treatment are in place. However, delivery of this continuum of care is inefficient in many jurisdictions (Gardner et al. 2011).

In this modeling study, we considered each single strategy separately. Previous analysis utilized an ordinary differential equation model to show that combining harm reduction with treatment interventions has a synergistic influence on reducing HIV incidence (Ramadanovic et al. 2013). Furthermore, optimizing the allocation of testing resources within the continuum of HIV care increases the number of HIV infections averted (Kok et al. 2015). The optimal HIV control strategy in the DTES would likely entail a specific mix of investments in harm reduction and treatment measures. We will study in future network model simulations the potential gains that could be achieved by combining optimization of resource allocation for HIV control and treatment strategies across the continuum of care.

Another area of interest for future work is network-based interventions. The strategies we describe in this paper are implemented homogeneously across the network. Details of network structure are not used to evaluate strategies targeted against individuals with a large number of contacts or high degree vertices in the network. "Network smart" control strategies are currently being studied. Evaluation of these types of control strategies requires model simulations of a more accurate underlying social network, such as the class of networks generated by the algorithm in Toivonen et al. (2006). Future work will also examine nonequilibrium response of the model over limited time horizons. This analysis will focus on the impact of control strategies on HIV incidence, because incidence is a better measure of the short-term response of an epidemic. Details of the social network structure are expected to be important for nonequilibrium analysis.

Our analysis demonstrates that network modeling can provide insight into control strategies for epidemics and serve as a potentially important tool for operational research applied to public health. However, our approach has several limitations and the network modeling approach in general has significant challenges in realistic applications. One issue relates to the motivation for our analysis to develop an operational strategy to control HIV in a specific setting. The epidemic in the Downtown Eastside neighborhood is shaped by a multitude of epidemiological, social, structural, and policy factors. Through extensive consultations and careful evaluation, we selected a subset of factors that are known to play critical roles in the epidemic. The model is necessarily complex to appropriately reflect the complexity of the epidemic. Nevertheless, simplifications were necessary to ensure reliability and tractability of the model. The most significant simplifying assumption is that the underlying social network in the model is a single network that was generated using the Barabási-Albert preferential attachment algorithm. More detailed analysis of the statistical properties of the social network is an important area for future work. The network structure in the model should also distinguish between injection drug user and sexual network edges, which are often but not always coincident. Another simplification was the assumption of a constant probability that injection drug use involves syringe sharing. With this assumption, the model does not have the capacity to evaluate situations where injection drug use and syringe sharing are decoupled and addressed through independent interventions. Transgender individuals were not included in the model, because of limitations in the data available. Data from additional cohort studies may be used to incorporate transgender individuals as a separate subpopulation in an expanded version of the model. A further simplification in the model is that HIV positive individuals are not diagnosed during the acute stage of infection. However, aggressive expansion of testing programs, combined with new types of tests that have a shorter testing window, increase the likelihood of acute stage diagnoses. The potential impact of more acute stage diagnosis will be examined in future work.

Network modeling also has general limitations. Network simulations typically require significant amounts of data and computational resources. For example, model calibration and analysis of the four intervention strategies studied in this paper required approximately 65,000 node-hours of computation on a cluster. However, network models are more structured than general agent-based models, which allowed us to incorporate generic information about social networks into the model. Furthermore, the body of

analytical results is much greater for network models, which provided a context in which to understand and verify our simulation model.

Extensive data are available on the HIV epidemic in Vancouver's Downtown Eastside, through detailed surveillance, monitoring programs and cohort studies. This provided us with the opportunity to evaluate whether a detailed network model of a real-world HIV epidemic could be developed and validated. The amount of data available to this project does not exist in most jurisdictions; however, we expect that the key lessons learned regarding the control of the HIV epidemic in Vancouver's Downtown Eastside may be relevant to HIV epidemics among injection drug users and sex workers in other settings. In particular, close connections between syringe sharing and sexual networks in closely linked communities deserve attention as potentially important avenues for rapid HIV transmission.

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