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Mathematical modeling of hepatitis C virus (HCV) prevention among people who inject drugs: a review of the literature and insights for elimination strategies

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Highlights:

- Governments are looking for guidance as to how to achieve the World Health Organization hepatitis C virus (HCV) elimination targets, particularly among people who inject drugs (PWID), a key risk group for HCV transmission
- Dynamic transmission modeling can help inform what level and type of intervention scale-up is required to reduce HCV incidence and chronic prevalence among PWID
- Modeling indicates that harm reduction alone is unlikely to achieve elimination targets among PWID.
- Modest levels of HCV treatment (<100 per 1000 PWID annually), particularly if combined with harm-reduction scale-up, can reduce HCV incidence among PWID by 80% by 2030 in a variety of settings
- Network-based treatment strategies as well as prison-based treatment and harm reduction provision could provide important population benefits.

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Title: Mathematical modeling of hepatitis C virus (HCV) prevention among people who inject drugs: a review of the literature and insights for elimination strategies

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Keywords: epidemic modeling, transmission, public health, infectious disease, hepatitis c virus, people who inject drugs

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Abstract: In 2016, the World Health Organization issued global elimination targets for hepatitis C virus (HCV), including an 80% reduction in HCV transmission by 2030. The vast majority of new HCV infections occur among people who inject drugs (PWID), and as such elimination strategies require particular focus on this population. As governments urgently require guidance on how to achieve elimination among PWID, mathematical modeling can provide critical information on the level and targeting of intervention are required. In this paper we review the epidemic modeling literature on HCV transmission and prevention among PWID, highlight main differences in mathematical formulation, and discuss key insights provided by these models in terms of achieving WHO elimination targets among PWID. Overall, the vast majority of modeling studies utilized a deterministic compartmental susceptible-infected-susceptible structure, with select studies utilizing individual-based network transmission models. In general, these studies found that harm reduction alone is unlikely to achieve elimination targets among PWID. However, modeling indicates elimination is achievable in a wide variety of epidemic settings with harm reduction scale-up combined with modest levels of HCV treatment for PWID. Unfortunately, current levels of testing and treatment are generally insufficient to achieve elimination in most settings, and require further scale-up. Additionally, network-based treatment strategies as well as prison-based treatment and harm reduction provision could provide important additional population benefits. Overall, epidemic modeling has and continues to play a critical role in informing HCV elimination strategies worldwide.

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- Modest levels of HCV treatment (<100 per 1000 PWID annually), particularly if combined with harm-reduction scale-up, can reduce HCV incidence among PWID by 80% by 2030 in a variety of settings
- Existing levels of testing and treatment are insufficient to achieve WHO goals and require scale-up
- Network-based treatment strategies as well as prison-based treatment and harm reduction provision could provide important population benefits.

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1. Introduction

The global burden of disease from viral hepatitis continues to rise; it became the seventh leading cause of death worldwide in 2013[1]. Among these deaths, a large majority were attributable to hepatitis C Virus (HCV) and hepatitis B virus (HBV). In response to this, in 2016 the World Health Organization (WHO) released targets for HBV and HCV “elimination as a public health threat” by 2030[2]. These targets include an 80% reduction in HCV infections, and a 65% reduction in HCV-related mortality, compared to a 2015 baseline. Governments are increasingly turning to epidemic models to inform prevention planning in terms of groups to be prioritized and levels and coverage required to meet these targets both at the country-level and among groups at higher risk.

HCV is a blood-borne virus which, if untreated, can result in liver cirrhosis, liver cancer, and death. In most developed and many developing countries, people who inject drugs (PWID) remain the main risk group for HCV infection, and as such are a priority group for prevention interventions[3]. The burden of HCV among PWID is high; globally an estimated 52% of PWID have a history of HCV infection[4]. As countries aim to prevent new HCV infections in order to reach the WHO elimination targets, a particular focus on preventing transmission among PWID is key.

No vaccine for HCV currently exists, although there are several highly effective harm reduction interventions to prevent HCV transmission. Opiate

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substitution therapies (OST), such as methadone and buprenorphine, reduce an individual's risk of HCV acquisition by 50% among PWID[5]. In combination, OST and high coverage needle and syringe programs (NSP) (receiving one or more sterile syringes for each injection), reduce an individual's risk of HCV acquisition by an estimated 74%[5].

In addition, to harm reduction interventions, treatment of chronic HCV also has a role to play in reaching elimination goals. The HCV treatment landscape has rapidly changed over the past few years, with the advent of highly effective direct-acting antiviral therapies which can achieve cure in >90% of individuals with short duration (8-12 week), and are all-oral, highly tolerable therapies. Alongside the worldwide interest in the use of HIV antiretroviral therapies for HIV prevention, these new HCV treatments have generated considerable enthusiasm that HCV treatment could be used for HCV prevention, with the added benefit that HCV treatment is finite and curative. As yet, no empirical studies have proven that scaled-up HCV treatment for PWID can result in reductions in population level HCV incidence or prevalence among PWID; however, a number of theoretical modeling studies have explored these potential population benefits by employing a dynamic transmission modeling approach.

Broadly, there are two approaches to estimating the population-level impact of treatment. Burden of disease models, which incorporate disease progression but not transmission, have shown that existing or modestly increased levels of treatment targeted at individuals with more advanced liver disease can

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achieve the WHO HCV mortality target (65% reduction by 2030) in a variety of settings[6]. These disease progression models are particularly valuable in identifying the level and targeting of treatment required to reduce HCV mortality, but because they do not mechanistically incorporate disease transmission, they are unable to shed light on what is required to achieve the WHO incidence elimination target. As such, they neglect the potential risk of reinfection but also the potential prevention benefit of treatment. An alternative to burden of disease models is dynamic transmission models, which mechanistically model disease transmission, and therefore incorporate the risk of reinfection in addition to the reduction in onward transmission associated with treatment.

In this paper, we review the existing literature surrounding HCV transmission and prevention modeling among PWID, with a focus on the general types of mathematical structures used, and insights related to achieving WHO elimination targets in this population group.

2. Methods

We performed a search on PubMed using the following search terms: ((hepatitis c) OR HCV) AND transmission AND (model OR modeling OR modelling) AND (inject* OR drug*). Abstracts were reviewed by 2 authors to determine eligibility. Original research studies which included dynamic HCV transmission models focusing on PWID were included in this review. Studies were included if they were in English.

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3. Modeling HCV transmission and elimination among PWID

Our review identified 67 relevant studies among 272 candidates, with details (author, year, setting, model type, and intervention examined) provided in **Supplementary Table 1**.

Early models of HCV epidemics among PWID utilized basic susceptible-infected (SI) formulations within a variety of modeling approaches (stochastic infividual-based and deterministic compartmental, HCV-monoinfection and HIV/HCV joint coinfection) to examine transmission dynamics in a range of theoretical and real-world settings [7-15]. These models simulated open populations, with injectors entering open initiation of injecting and exiting the PWID population through permanent cessation of injecting or death. In all models, HCV transmission was represented through sharing of unsterile syringes or injecting paraphernalia.

A simple example deterministic model equation is presented below, compartmentalizing the PWID population into HCV uninfected (S(t)) and those with chronic HCV (C(t)).

$$\frac{dS(t)}{dt} = \theta - \pi(1-\delta)\frac{C+Z}{N}S - \mu S \qquad 1.1$$

$$\frac{dC(t)}{dt} = \pi(1-\delta)\frac{C+Z}{N}S - \mu C \qquad 1.2$$

The total population is denoted by *N(t)*, where *N(t) = S(t)+ C(t).* PWID enter the model at a fixed rate, θ, and can exit any of the compartments either due

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to injection cessation or death at a rate, μ. The force of infection is proportional to the infection rate, π, prevalence of infection, and the susceptible population. In general, models assume that PWID mix proportionally, although some explore assortative mixing by risk or age. A proportion (δ) of those infected with acute infections will spontaneously clear (in other words, self-cure) their acute infection and remain susceptible. The remaining proportion ($1-\delta$), will progress to chronic infection. Models often include additional stratification due to risk or age. Due to the observation of stable HCV prevalence in the majority of documented settings, nearly all models simulate the HCV epidemic starting at equilibrium.

These early generally examined the impact of changes in injecting risk, disconnected with real-world interventions. Although there is currently no vaccine for HCV, some compartmental modeling studies evaluated the impact of a theoretical HCV vaccine on transmission by incorporating an immune population stratification[16, 17]. As evidence supporting the efficacy of harm reduction (OST and NSP) on HCV transmission emerged[5], combined with the availability of highly effective curative HCV treatment, modeling studies primarily focused on assessing the impact of these interventions on HCV transmission.

3.1. Modeling the impact of harm reduction

Several studies quantify the substantial impact existing harm reduction interventions such as opiate substitution therapy (OST) and needle and syringe programs (NSP) have had on population incidence and prevalence

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among PWID[18-23]. This was generally implemented though the incorporation of model stratification by harm reduction coverage status (e.g. no OST or NSP, only OST, only NSP, both OST and NSP). PWID usually enter with no harm reduction coverage, and can be recruited or drop-out of each intervention. While on an intervention, PWID experience a reduced risk of injecting transmission and acquisition while on these interventions Example model equations for a deterministic model incorporating these features can be found in in the supplementary information.

Despite the effectiveness of OST and NSP in preventing HCV acquisition, several epidemic modeling studies have shown that harm reduction alone is unlikely to be sufficient to achieve HCV elimination among PWID[18, 19]. For example, a study by Vickerman et al. in the UK indicated that high levels of existing harm reduction (>50% coverage of OST and NSP among PWID) likely averted a very high burden of HCV among PWID (>80%, compared to ~40% prevalence currently). Further increases in coverage, however, would only have modest impact on the HCV epidemic among PWID[18]. Another analysis by Martin and colleagues examined three generic prevalence settings of HCV among PWID (20%, 40%, and 60% chronic HCV among PWID) and similarly found that scaled-up harm reduction (either in settings with no existing harm reduction or those with existing levels) would not be sufficient to reduce HCV incidence to the WHO target levels of 80% reduction in any setting[19].

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In part, this is because combined harm reduction is not fully effective at preventing HCV acquisition, and also because the average time on harm reduction (1 year or less on OST for example) means that many PWID experience periods of being at high risk of HCV acquisition during times out of contact with harm reduction services[24]. As HCV is highly transmissible (10-fold more infectious than HIV), the majority of PWID are infected with HCV within the first 2 years of their injecting career[25]. This means that harm reduction must reach people early on in their injecting career to maximize prevention benefit, and also that maintaining full harm reduction coverage for an individual over their entire injecting career (with an average PWID injecting for 10+ years) poses a significant challenge. Nevertheless, due to the multiple benefits of harm reduction aside from HCV acquisition prevention (including benefits related to HIV transmission and incarceration), OST and NSP should form the backbone of HCV prevention for PWID.

3.2. Modeling HCV treatment as prevention

In this section, we describe the basic mathematical approaches to treatment as prevention epidemic modeling (section 3.2.1), the general findings (section 3.2.2.), and specific subsections on modeling implications for *whom to target* for elimination, such as network-based targeting (section 3.2.3), incarcerated individuals (section 3.2.4), and HIV/HCV coinfected individuals (3.2.5).

3.2.1 Treatment as prevention modeling approaches

Several research teams have utilized dynamic models of HCV transmission among PWID to explore the impact of scaled-up HCV treatment as prevention

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in a range of settings including North America, Europe, Asia, and Australia[15, 17, 19, 24, 26-60]. These studies generally incorporate a similar deterministic susceptible-infected-susceptible (SIS) compartmental model structure, though some have used stochastic individual-based models[27, 34-37, 43, 53, 54, 61]. All of these studies incorporate the risk of reinfection after successful treatment. A simple example deterministic model schematic is shown in **Figure 1**, extending the model equations (1.1 and 1.2) to incorporate PWID on treatment (T(t)), and PWID who failed treatment (Z(t), who are or are not eligible for retreatment depending on the model). The associated equations for the simple HCV dynamic transmission model in **Figure 1** are presented below:

$$\frac{dS(t)}{dt} = \theta - \pi(1-\delta)\frac{C+Z}{N}S + \omega\alpha T - \mu S \quad 2.1$$

$$\frac{dC(t)}{dt} = \pi(1-\delta)\frac{C+Z}{N}S - f(C) - \mu C \quad 2.2$$

$$\frac{dT(t)}{dt} = f(C) - \omega T - \mu T \quad 3.3$$

$$\frac{dZ(t)}{dt} = \omega(1-\alpha)T - \mu Z \quad 4.4$$

The total population is denoted by *N(t)*, where *N(t) = S(t)+ C(t)+ T(t)+ Z(t).* Chronically infected PWID can be treated through a function f(C) which can change over time. Generally, models have assumed that a fixed number of PWID are treated per year, e.g. f(C)= ϕ if ϕ <C, and f(C)= C if ϕ >=C. PWID who are treated remain on treatment for a period of time,$1/\omega$, and are generally not assumed infectious due to substantial reductions in viral loads during treatment, even for the small proportion who ultimately fail treatment.

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After treatment, a proportion (α) will obtain sustained viral response, or cure, and become susceptible again. All of the studies mentioned above included a potential risk of reinfection after successful treatment, generally assuming that the risk of reinfection among a particular risk group is the same as primary infection, and therefore not including behavior change after treatment. The remaining proportion (1-α) fail treatment and move to the treatment failure group, who in this model are not eligible for retreatment.

3.2.2 Treatment as prevention modeling findings

Early studies by Martin and colleagues provided important theoretical evidence that modest levels of HCV treatment for PWID could dramatically reduce HCV prevalence over short timescales (5-10 years), despite the risk of reinfection[31, 57, 62]. Subsequently, numerous groups examined the impact of HCV treatment in a range of global settings[15, 17, 19, 24, 26-60].. Overall, despite heterogeneities in terms of epidemic characteristics between these global settings, these studies have generally found that scaled-up HCV treatment rates of below 100 per 1000 PWID annually, particularly in combination with harm reduction[19, 27, 30, 56, 59, 63], can reduce HCV incidence by >80% by 2030. This is summarized in **Figure 2,** which shows the level of HCV treatment scale-up required to reduce HCV incidence by 80% across three settings with varied burden of HCV among PWID (20%, 40%, and 60% chronic HCV among PWID), with or without various levels of harm reduction scale-up. Coordinated scale-up of harm reduction has the benefit of reducing the numbers of treatments required due to the primary prevention

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benefit of harm reduction, and also through the prevention of reinfection after successful treatment.

However, despite these studies indicating that only modest levels of HCV treatment are required to achieve elimination targets, and several studies that HCV treatment for PWID is cost-effective when incorporating transmission prevention benefits[49, 50, 64-66], it appears that in many settings (with the exception of France[37]), current testing and treatment rates for PWID are too low to generate measurable declines in HCV prevalence or incidence[44, 45, 67].

For example, a modeling study across multiple sites in the U.K. found that current treatment rates (varying from less than 5 to 26 per 1000 PWID per year) are likely insufficient to lead to observable declines in HCV prevalence in a decade in all of the seven sites examined, particularly given the substantial uncertainty in several important parameters (such as prevalence of injection drug use and chronic HCV prevalence)[44]. This was further supported by an analysis in 11 European settings, which indicated that current treatment rates among PWID are likely to achieve observable reductions in chronic prevalence in 10 years in only 3 of the 11 sites (Czech Republic, Slovenia, and Amsterdam)[45]. Similar results have been found in Iceland[56], Montreal, Canada[36], Vancouver Canada[68], and a multi-site analysis in Edinburgh (Scotland), Vancouver (Canada), and Melbourne (Australia)[24]. In none of the global settings examined were existing testing and treatment rates sufficient to achieve WHO elimination targets, indicating the need for

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widespread scale-up of testing, treatment and harm reduction for PWID.

Some settings will likely pose a greater challenge to elimination strategies. Settings with higher incidence or prevalence require higher testing and treatment rates in order to achieve elimination compared to epidemics with lower burden of disease[19, 24, 69]. Modeling studies in areas with very high burden of disease, such as in Athens, Greece (where >80% PWID have a history of HCV infection, and an estimated 65% are chronically infected with HCV), have tended to focus on the importance of a combination prevention approach[27]. Additionally, a recent modeling analysis focusing on a setting in the rural U.S. with very high and increasing incidence (>40 per 100 person-years) indicated that although elimination was still achievable through scaling up harm reduction (to 50% coverage among PWID) in combination with treatment rates of 89 per 1000 PWID annually, the treatment rate required was 3-fold higher than in a setting with stable incidence[70].

Finally, the high cost of DAA therapy and the dual HCV elimination goals of reducing incidence and HCV-related mortality has led to several studies examining the impact and cost-effectiveness of various HCV treatment prioritization strategies. A modeling study in Scotland highlighted that strategies focusing on HCV-related mortality would likely prioritize older individuals with more advanced liver disease who are unlikely to still exhibit ongoing injecting risk, whereas strategies targeting incidence would prioritize younger PWID with less advanced fibrosis and less immediate risk of HCV-mortality[71]. General-population based models incorporating PWID

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transmission have further explored the impact of HCV treatment prioritization strategies, with an analysis in Pakistan showing that prioritizing treatment to PWID and those with cirrhosis would reduce the number of treatments required for achieving both elimination targets, but that broader reductions in transmission risk are required due to the generalized nature of the epidemic[72].

3.2.3 Who to target: Network-based treatment as prevention strategies?

Several modeling studies have addressed the question of *whether network-based treatment targeting approaches* could maximize prevention benefits, using empirically derived individual-based network models. Hellard and colleagues published a series of stochastic individual-based network models of HCV transmission of PWID calibrated to detailed injecting network data among PWID in Melbourne, Australia[33, 34, 43, 54]. These studies used exponential random graph models (ERGMs) to simulate injecting relationships, and assume static networks. ERGMS are a type of exponential model that assume that the structure of the observed network can be statistically inferred. They treat nodes (individuals) as fixed and model the process underlying the observed network structure[73]. These studies compared efficacy of network-based interventions among PWID, including ring vaccination with secondary contacts on reducing HCV incidence. They found strategies that treat PWID and all of their contacts (analogous to ring vaccination) are most effective at reducing the incidence rates of re-infection and combined infection, and were more effective than random treatment. Conversely, strategies targeting infected PWID with the most contacts

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(analogous to targeted vaccination) are the least effective.

However, in a recent U.S.-based publication, Zelenev and colleagues calibrated an individual-based network model of HCV transmission to data among PWID in Hartford, Connecticut[74]. They compared treating a randomly selected PWID versus an individual with the highest number of injection partners, treating either none, half, or all of the injection partners of the selected individual, as well as a respondent-driven recruitment into treatment. In contrast to Hellard et al., this study found a random treatment allocation most effective, likely due to differences in network characteristics between these two settings.

Overall, these studies highlight the differences in impact depending on network structure, which was confirmed by a recent theoretical network-based analysis indicating the sensitivity of treatment as prevention impact to the assumed network contact structure[61]. In general, it is likely that the importance of the injecting network will vary substantially by setting, and more data are required to inform the utility and importance of network-based treatment as prevention strategies for elimination.

3.2.4 Who to target: Incarcerated individuals?

Due to the criminalization of drug use, there is a high prevalence of PWID in prison, and substantial interest in incarcerated populations as a priority target for HCV prevention interventions. Globally, 10-48% of males and 30-60% of female inmates have used illicit drugs in the month before entering prison[75], and 50-90% of PWID have ever been incarcerated[76]. As such, prison could

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serve as an important access point to treat HCV and provide prevention interventions among PWID. Several deterministic compartmental studies have explored the potential impact of prison-based HCV prevention strategies on the community epidemic in the U.S. and U.K. These studies explicitly stratify the population by incarcerated status (such as never incarcerated, incarcerated, previously incarcerated), such that PWID who are incarcerated are assumed to only share syringes with other incarcerated PWID. A modeling and cost-effectiveness analysis in England found that opt-out HCV testing and treatment in prison is likely cost-effective, but would have minimal community epidemic impact due to low treatment rates for PWID and gaps in the cascade of care from testing to cure[46]. A modeling analysis in Scotland similarly found that continuing existing levels of prison treatment would have minimal impact, reducing HCV incidence by a relative 11% (95%CrI 8-13%) among community PWID in the next 15 years. However, if prison HCV treatment were scaled-up to 80% of chronically infected PWID prison entrants with sentences >16 weeks, HCV incidence among community PWID could reduce by a relative 46% (95%CrI 38-51%) in 15 years[47]. As such, scaled-up treatment in prison could at least, in theory, have substantial prevention benefit. This assertion is also supported by modeling in the United States which indicates that a one-time opt-out prison HCV testing campaign, combined with behavior change after diagnosis, high uptake of treatment, and behavioral risk reduction after treatment, could avert a substantial number (~8,000) of HCV infections, the vast majority among PWID in the community[48]. Additional studies have examined the potential impact of prison-based harm reduction [77], suggesting OST in prison and on release

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could avert more than 50% of new infections in settings with incarceration patterns like Scotland, Australia, and Thailand. Overall, modeling indicates prison could be an important point of engagement of PWID and setting for HCV prevention.

3.2.5 Who to target: HIV/HCV coinfected subpopulations?

Policymakers and funders are increasingly interested in the concept of 'microelimination', or elimination within defined geographical areas or subpopulations. Among these, recent interest has focused on HIV/HCV coinfected populations as a priority group for elimination given that coinfection with HIV accelerates HCV disease progression and mortality. Several modeling studies have modeled joint HIV and HCV coinfection transmission dynamics among PWID[78-81], but few examine HCV prevention and elimination specifically. These studies incorporate both HIV and HCV transmission, as well as interactions between the two infections (such as HIV-infection reducing and individual's risk of HCV spontaneous clearance and increasing and individual's HCV transmissability due to elevated HCV viral load). One theoretical study examined the impact of prioritization of treatment and behavioral risk reductions on HIV and HCV among PWID, showing differential impact on HIV and HCV epidemics depending on whether low or high risk PWID were targeted[82]. A compartmental model of HCV transmission among HIV+ infected populations only (stratified by risk) from France indicated that elimination among HIV+ individuals is achievable by targeting HIV/HCV coinfected individuals only, but this model did not incorporate the full transmission dynamics from the HIV-uninfected population

and so may underestimate the risk of infection/reinfection among HIV+ PWID with ongoing risk[83]. Indeed, a recent HIV/HCV coinfection transmission modeling study based in Andalusia, Spain, has indicated that although targeting HIV/HCV coinfected PWID for treatment could reduce the prevalence of HCV among HIV+ PWID and all PWID, continued infection (and reinfection) from the HCV-monoinfected population means that HCV elimination among HIV-positive PWID requires scaled-up prevention efforts among both the HIV-coinfected and HCV-monoinfected population alike[84].

4. Discussion

As global interest turns to achieving the WHO HCV elimination targets, governments are increasingly relying on mathematical models to inform their prevention strategies and resource allocation. Dynamic HCV transmission models can provide critical information on what intervention type, level, and targeting is required to achieve WHO elimination targets. PWID remain a key priority group for treatment and prevention interventions given their important role in HCV transmission in many developed and developing country settings. In this paper, we review the increasingly broad body of literature has utilized dynamic transmission models to assess what is required to reduce HCV chronic prevalence and incidence among PWID, and what strategies could achieve WHO elimination targets. Previous reviews of HCV transmission among PWID either were performed prior to the WHO elimination goals[85] or focused on recent literature and were not comprehensive[86].

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Generally speaking, these models indicate that modest and achievable levels of HCV treatment scale-up to PWID, particularly if combined with scaled-up harm reduction, could achieve the WHO elimination goals in a wide variety of settings. These findings have been robust to the variety of modeling structures used (both deterministic compartmental and individual network-based). Notably, however, network-based models indicate that substantial heterogeneity in impact is achieved depending on the assumed network structure. Given the paucity of studies utilizing real-world network data which have been limited to high income settings, the need for additional further epidemiological and modeling studies is warranted.

Gaps within the existing literature include a lack of models examining developing country settings. The vast majority of existing models examine settings in Europe, the United States, and Australia. Only two models have examined low-middle income country settings (Vietnam and Pakistan)[10, 40]. More studies examining developing country settings are needed as the majority (estimated 80%) of the global burden of HCV infection falls within low-middle income country settings[87].

The models are additionally limited by uncertainty in their underlying data. Substantial uncertainty in relation to HCV incidence and prevalence among PWID generates uncertainty in the level of intervention scale-up required to achieve elimination goals, with modeling indicating that higher burden settings require greater intervention scale-up. However, uncertainty in HCV incidence also adds to complexity in terms of measuring outcomes, as models may

predict declines in incidence or prevalence which may not be statistically measurable. Furthermore, there is uncertainty in other parameters which alter estimates of intervention impact, such as average duration of injecting and number of PWID in a given setting. More robust data on these measures will help reduce uncertainty and increase accuracy of the mathematical models.

One additional key area of uncertainty is the impact of HCV diagnosis and treatment on behavior change. The majority of models do not assume any change in behavior after diagnosis or treatment. However, if HCV diagnosis or treatment results in reduced injecting risk behavior, then the impact of testing and treatment interventions could be even greater than predicted by existing models.

Finally, it is important to reiterate that, to date, there is no empirical evidence that HCV treatment for an individual can lead to population prevention benefits. Existing evidence of treatment as prevention impact is limited to theoretical modeling studies only. Several existing trials are in the process of generating empirical evidence of treatment as prevention. For example, one study in Australia (Surveillance and Treatment of Prisoners for Hepatitis C, STOP C), is examining the impact of HCV treatment in prison on HCV incidence among incarcerated populations in New South Wales. Another study in Scotland (ERADICATE) is measuring the impact of scaled-up HCV treatment in Dundee, Scotland, on community HCV incidence and prevalence among PWID. These studies will generate important real-world evidence of treatment as prevention impact. Additionally, many of these models neglect

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the practical challenges which may arise during implementation of treatment scale-up. Indeed, a modeling study in Australia indicated that increased testing/diagnosis among PWID is required in order to reach elimination targets, not simply expansion of treatment among those diagnosed[88].

5. Conclusion

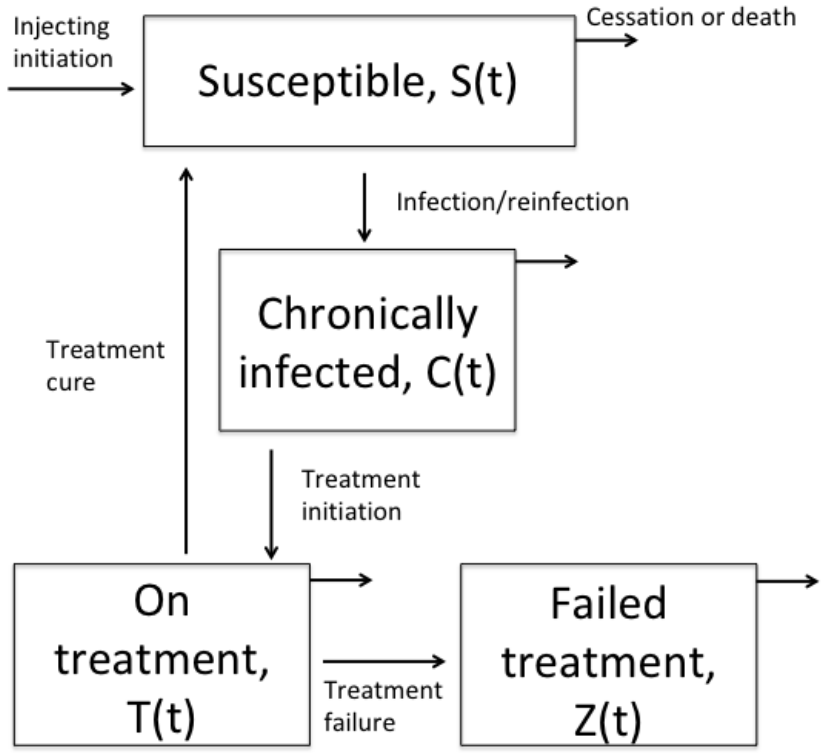
The possibility of elimination of HCV as a public health threat is generating tremendous worldwide interest. As countries develop plans to achieve the ambitious WHO goals of an 80% reduction in HCV incidence and 65% reduction in HCV-related mortality by 2030, they seek guidance on how best to achieve these targets. Epidemic modeling studies provided the first theoretical evidence that HCV treatment as prevention strategies could achieve substantial reductions in prevalence/incidence despite the risk of reinfection, and in combination with harm reduction provide a critical component of the elimination response. These models have subsequently have provided key insights into the type and level of intervention scale-up required to achieve these targets. Broadly speaking, it is clear that current strategies prioritizing treatment to those with advanced liver disease, at the expense of providing treatment to PWID (the majority who are younger with less advanced disease), will hamper progress towards elimination.

Additional scale-up of HCV testing, treatment, and harm reduction services are required to meet these ambitious WHO targets. Strategies which prioritize intervention to key sub-groups such as incarcerated individuals and injecting-network partners could provide more impact and achieve elimination faster. More work is needed in low-middle income country

settings, and examining the impact of interventions to increase testing and linkage to care. Future empirical studies are required to test whether scaled-up HCV treatment for those at risk of transmission can lead to population benefits in terms of reduction in HCV incidence. These epidemic studies can be combined with economic analyses to determine both the optimal impact, but also cost-effectiveness and budgetary impact of HCV elimination strategies, better informing the worldwide public health response.

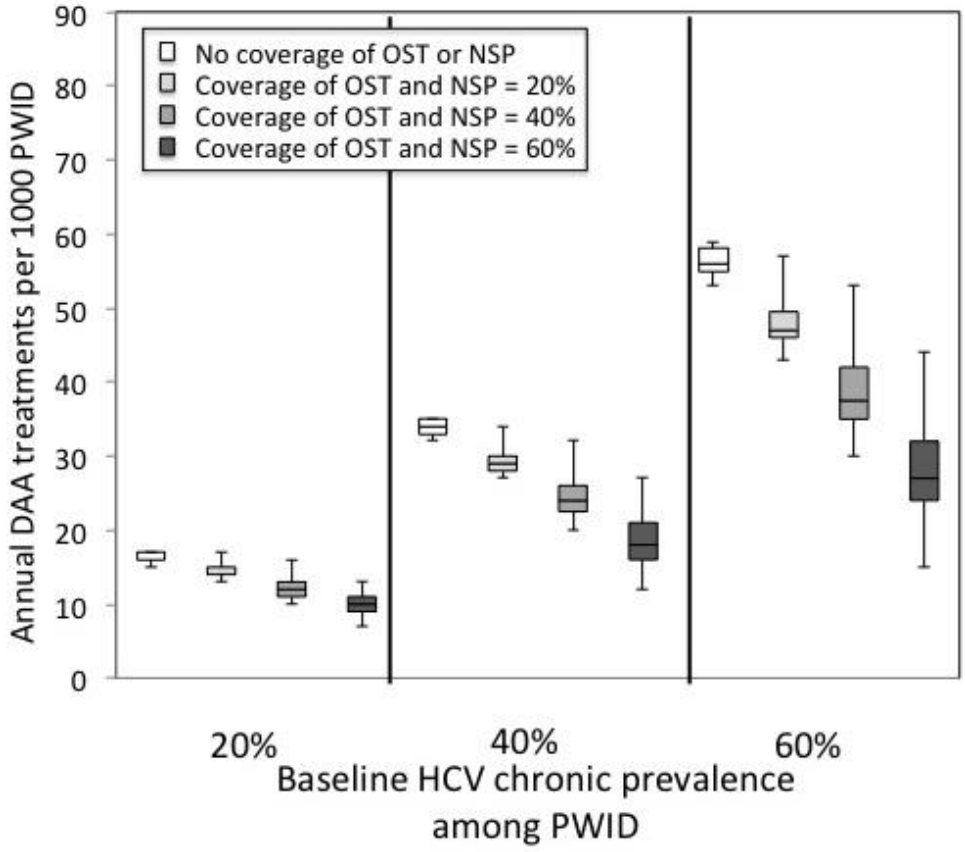
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Figure 1. Example schematic for a simple HCV transmission epidemic model among PWID.



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Figure 2. Levels of combination prevention required to achieve WHO elimination targets (80% reduction in incidence by 2030) among PWID populations in various settings (20/40/60% chronic HCV among PWID). Results show the coverage of HCV DAA therapy (y axis) combined with different levels of harm reduction (white and gray boxes) required to reduce HCV incidence by 80% from 2018-2030 across three settings with varied baseline chronic HCV among PWID (20%/40%/60%). Updated simulations from Martin based on a previously published model[19].



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