Agent-based modeling of persons who inject drugs in metropolitan Chicago suggests that re-treatment with antivirals of persons who are re-infected with Hep C is critical to achieve the WHO incidence reduction objective by 2030

Eric Tatara[1*@], Alexander Gutfraind[2,3*], Nicholson T. Collier[1], Scott J. Cotler[2], Marian Major[4], Basmattee Boodram[3†], Jonathan Ozik[1†], Harel Dahari[2†]

(1) Consortium for Advanced Science and Engineering, University of Chicago, Chicago, IL; Decision and Infrastructure Sciences, Argonne National Laboratory, Argonne, IL, USA; (2) The Program for Experimental & Theoretical Modeling, Division of Hepatology, Department of Medicine, Loyola University Medical Center, Maywood, IL, USA; (3) Division of Community Health Sciences, School of Public Health, University of Illinois at Chicago, Chicago, IL, USA; (4) Division of Viral Products, Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, USA.

*Contributed equally to this study; †Co-senior authors; @Corresponding author. tatara@anl.gov

Running Title: Agent-based modeling of persons who inject drugs

ABSTRACT

Hepatitis C (HCV) is a leading cause of chronic liver disease and mortality worldwide. Persons who inject drugs (PWID) are at the highest risk for acquiring and transmitting HCV infection. We developed an agent-based model (ABM) to identify and optimize direct-acting antiviral (DAA) therapy scale-up and treatment strategies for achieving the World Health Organization (WHO) goals of HCV elimination by the year 2030. DAA is highly efficacious, but may require re-treatment particularly among PWID who at risk for reinfection after cure. Using an ABM approach, we predict that this prohibition will jeopardize achieving the WHO's goal of reducing 90% of HCV incidence by 2030. We found that DAA scale-up rates of greater than or equal to 5% per year can achieve the WHO target of 90% incidence reduction. Our model simulations underscore the importance of DAA scale-up that includes re-treatment of re-infected individuals in order to achieve significant reductions in incidence.

Key words: Hepatitis C virus; persons who inject drugs; Agent-based modeling; direct-acting antivirals, incidence reduction;

FUNDING

This research is supported by NIH grant R01GM121600.

INTRODUCTION

Persons who inject drugs (PWID) are at the highest risk for acquiring and transmitting hepatitis C virus (HCV) infection [1]. Approximately 32,000 PWID reside in metropolitan Chicago, Illinois with an estimated HCV-RNA prevalence of 47% [2]. We previously developed an agent-based model (ABM) to simulate the PWID population in metropolitan Chicago including the social interactions that result in HCV infection, and applied this to study and predict changes in HCV prevalence in this population [3]. In our present study we have ported the ABM to our Hepatitis C Elimination in PWID (HepCEP) model to identify and optimize direct-acting antiviral (DAA) therapy scale-up and treatment strategies for achieving the World Health Organization (WHO) goals of reducing new chronic infections by 90% by 2030. While DAA treatment is highly efficacious, some payors still restrict access to DAAs [4] and in particular prohibit DAA re-treatment of those who become re-infected once cured by DAA therapy. We examined whether this prohibition may jeopardize achieving a >90% reduction in HCV incidence by 2030 as proposed by the WHO.

METHODS

We extended the capabilities of our previous ABM [3] to include DAA therapy and large-scale simulated parameter sweeps over DAA scale-up rates with the Repast HPC-based [5] HepCEP model. Re-treatment prohibition of individuals who are treated once and re-infected is examined specifically in the context of achieving significant reductions in HCV incidence.

Treatment enrollment is modelled as unbiased sampling of HCV RNA positive PWIDs such that infected individuals are sampled at random from the total PWID population. The enrollment rate per 1000 per year is a model parameter that determines the total treatment enrollment at a given time, as a fraction

of the total population. We model a treatment duration of 12 weeks. Treatment success probability is a function of treatment non-adherence and sustained virologic response (SVR) parameters. We use a treatment failure rate of 10% and treatment SVR of 90%. Treatment re-enrollment prohibition is modelled via a Boolean model parameter that allows or disallows PWID from being re-selected for treatment enrollment after completing a successful treatment and becoming re-infected. DAA cost is assumed $25,000 (USD) per treatment.

To examine the effects of re-treatment prohibition and enrollment rate scaleup, a series of simulations was conducted using high-performance computing workflows implemented with the EMEWS framework [6]. This runs on the Bebop cluster at the Laboratory Computing Resource Center at Argonne National Laboratory. A group of five scenarios were simulated with different enrollment rates (0%,2.5%,5%,7.5%,10%) with 20 stochastic replicates each for DAA scale-up without re-treatment and the same five enrollment rate scenarios were simulated with 20 stochastic replicates each with re-treatment. Each simulation requires approximately 1.5 hours of wall time to complete. Using the EMEWS workflow on the Bebop cluster, the actual compute time is close to 1.5 hours since all runs can execute in parallel.

The simulation start date of 2010 was selected based on the PWID demographic data from multiple surveys in previous years [3]. The model time step is one day, and treatment enrollment is started in year 2020 and run until year 2030, with detailed model data collected on daily intervals. We report the mean incidence per 1000 person-years relative to the mean baseline incidence rate in year 2020 with no treatment (enrollment rate of 0%). The mean incidence rate and 95% confidence interval on mean incidence rate is determined from the 20 stochastic runs.

RESULTS/DISCUSSION

Model results in all PWID populations with re-treatment prohibition

While unbiased (i.e., random) DAA scale-up rates of greater than 3% per year would lead to a dramatic decline in HCV RNA prevalence (not shown), relative HCV incidence was projected to increase during the

first several years of initiation of DAA scale-up due to the increase in availability of susceptible PWID who can acquire HCV (Fig. 1A). The initial increase in HCV incidence will then be followed by a transient decline in incidence which settles just below a nominal relative rate of 1.0 (Fig. 1A).

Model results in all PWID populations without re-treatment prohibition predict that:

An unbiased DAA scale-up rate of 2.5% per year is not sufficient to reduce HCV incidence (Fig. 1B). However, DAA scale-up rates of greater than or equal to 5% per year can achieve the WHO target of 90% incidence reduction with a total DAA cost of $316 million (Fig. 1B,C). The treatment enrollment rate of 5% indicates that the majority of PWIDs (55%) only enroll once, with 28% enrolling twice, and 16% of PWID enrolling three or more times (Fig. 1C,D).

Recently, using an ordinary differential equation (ODE) modeling approach [7] we predicted that a DAA scale-up rate of 4.5% at a cost of $461 million is needed to reach >90% reduction of incidence over 15 years. To reach >90% reduction in incidence within 10 years (ie., by 2030), the ODE model estimates a minimal scale-up of 6.6% at a cost of $430 million (unpublished data), compared to 5% scale up using HepCEP at a lower DAA cost of $316 million, as noted above. The results indicate that the ODE approach is an overestimate of the actual needed cost to reach >90% reduction, which is to be expected because it does not represent the network structure of the PWID population which modulates the transmission. The ABM modeling approach is likely to be more suitable than ODE modeling for predicting the effects of any barriers to treatment.

HepCEP model simulations underscore the importance of DAA scale-up that includes re-treatment of re-infected individuals in order to achieve significant reductions in incidence. Re-treatment, which can reduce/eradicate viral titers as many as seven times for the same person (Fig. 1C,D), is predicted to be highly efficacious to curtail transmission (i.e., reducing incidence) in agreement with our recent modeling

predictions [8]. An unbiased DAA scale-up of 5% (or 50 per 1000 PWID) per year is projected to achieve the WHO target of 90% incidence reduction by 2030 (Fig. 1B).

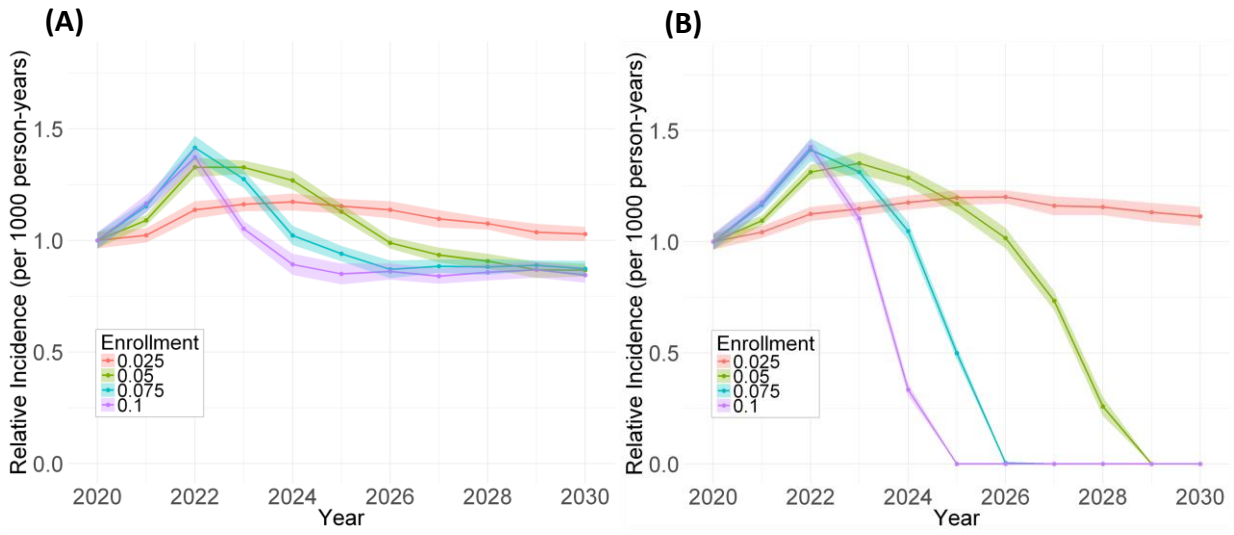
HepCEP considers both re-infections and unsuccessful treatments (failure to achieve SVR) in the re-treatment prohibition scenario (Fig. 1A), however the model may be configured to only prohibit re-treatment in re-infection cases. In this scenario, the relative HCV incidence (not shown) can be further reduced somewhat compared to the stricter re-treatment policy, however the relative incidence still cannot be reduced below 0.5 with an enrollment rate of 10%, underscoring that re-treatment of HCV re-infections is needed to achieve the desired reduction in incidence. Further HepCEP model explorations that include additional intervention strategies (e.g., harm reduction) and DAA scale-up rates are needed to predict the most feasible and cost-effective strategies for achieving HCV elimination among PWID.

REFERENCES

1. Bruggmann, P., *Treatment as prevention: the breaking of taboos is required in the fight against hepatitis C among people who inject drugs.* Hepatology, 2013. **58**(5): p. 1523-5.
2. Tempalski, B., et al., *Trends in the population prevalence of people who inject drugs in US metropolitan areas 1992-2007.* PLoS One, 2013. **8**(6): p. e64789.
3. Gutfraind, A., et al., *Agent-Based Model Forecasts Aging of the Population of People Who Inject Drugs in Metropolitan Chicago and Changing Prevalence of Hepatitis C Infections.* PLOS ONE, 2015. **10**(9): p. e0137993.
4. Ooka, K., J.J. Connolly, and J.K. Lim, *Medicaid Reimbursement for Oral Direct Antiviral Agents for the Treatment of Chronic Hepatitis C.* Am J Gastroenterol, 2017. **112**(6): p. 828-832.
5. Collier, N. and M. North, *Parallel agent-based simulation with Repast for High Performance Computing.* SIMULATION, 2013. **89**(10): p. 1215-1235.
6. Ozik, J., et al. *From desktop to Large-Scale Model Exploration with Swift/T*. in *2016 Winter Simulation Conference (WSC)*. 2016.
7. Echevarria, D., et al., *Modeling indicates efficient vaccine-based interventions for the elimination of Hepatitis C virus among persons who inject drugs in metropolitan Chicago.* Vaccine, 2019(Accepted for publication).
8. Major, M., et al., *Modeling of patient virus titers suggests that availability of a vaccine could reduce hepatitis C virus transmission among injecting drug users.* Science Translational Medicine, 2018. **10**(449): p. eaao4496.

CONFLICT OF INTEREST

All authors declare that they have nothing to disclose.



(C)

Treatment Frequency	No. PWID	No. Treatment Episodes	Treatment Episodes %	DAA Cost (1K $)
1	6943	6943	54.8	173,575
2	1780	3560	28.1	89,000
3	478	1434	11.3	35,850
4	128	512	4.0	12,800
5	31	155	1.2	3,875
6	8	48	0.4	1,200
7	2	14	0.1	350
Totals	9370	12666	100	316,650

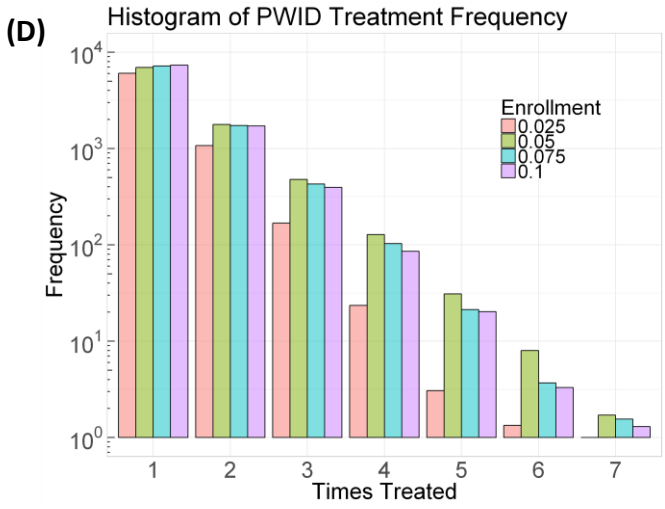


Figure 1. Projected relative HCV mean incidence among PWID relative to the predicted 2020 incidence during DAA scale-up (enrollment is DAA scale-up rate e.g., enrollment of 0.1 indicates scale up of 10% (or 100 per 1000 PWID) per year). (A) Without re-treatment. (B) With re-treatment. The ribbons represent the 95% confidence interval around the mean. (C) Mean PWID treatment enrollment frequency and DAA costs distribution for DAA scale-up rate of 5% per year without re-treatment prohibition. Percent treatment is calculated as the fraction of each frequency No. treatments over all treatments, and the DAA cost per treatment is $25,000. (D) Distribution of treatment enrollment count per PWID without re-treatment prohibition for various DAA enrollment rates.