**Optimized strategies of HCV treatment among substance users**

## **Introduction**

Treatment of HCV infections has been revolutionized with the introduction of highly-potennt antivirals. These antivirals can be given as oral pills and over a 6-12 week treatment achieve cure rates of 95% or higher. Using these antivirals it would be possible to irradicate HCV in rich countries. The treatment could even be introduced in populations that experience very high prevalence of HCV, particularly people who inject drugs (PWID).

Because of the high cost of large scale interventions, it is valuable to perform detailed studies that estimate the likely results in terms of treatment cost and impact on HCV prevalence. Several studies have examined the implementation of HCV treatment in PWID, including one by our team[[1]](#footnote-2). However, with some exceptions (REF) the studies model the PWID population using a differential-equation models (ODEs). Although ODEs can provide valuable insights into disease dynamics, they aggregate the population to a small system of equations. As a result of this aggregation, there is a loss of realism and all details about the geography, network and individual characteristics are not considered.

An agent-based modeling strategy, which represents each individual in the population and their health and behavior, allows a more realistic assessment of the impacts of a large-scale anti-HCV intervention. Therefore, in this paper we examine the likely outcome of a large-scale HCV treatment program targeting the PWID population. Our study examines:

1. The efficacy of various recruitment strategies of PWID
2. The tradeoff between cost (scale of recruitment) and HCV prevalence
3. Optimize the implementation of the study to better achieve public health outcomes and reduce the cost

## **Methods**

In this study we extend our previous research into modeling of HCV infections among PWID[[2]](#footnote-3). The previously developed agent-based model, termed APK was extended to incorporate (1) recruitment for treatment, (2) HCV dynamics during treatment, (3) TBD

This document describes *completed* changes to the APK software to account to HCV treatment with directed-acting antivirals (DAAs).

Additional changes / modifications are possible.

**Table AV: Antiviral treatment parameters. Values are tentative.[[3]](#footnote-4)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **Value** | **Range** | **Range and References** |
| treatment\_enrollment\_rate | 10 per 1000 | varied in simulations | [0, 1000] |
| treatment\_enrollment\_start\_delay | 2190 days |  | Effective start is 2016/1/1  based on simulation start of 2010/1/1 |
| treatment\_enrollment\_method | Fraction of recruitment by method | varied in simulations | p\_U, p\_HR, p\_FN, p\_IN, p\_OUT (see *explanation of recruitment methods*) |
| mean\_days\_residual\_hcv\_infectivity | 5 days [[4]](#footnote-5) | 3-7 | [3,30] |
| treated\_susceptibility | 100% | 0.95-1.00 | (REF) |
| treatment\_duration | 84 days (12 weeks) |  | (REF) |
| treatment\_non\_adherence | 10% | 0.05-0.15 | Citation needed |
| treatment\_repeatable | False |  | Due to cost, treatment is available only once (REF) |
| treatment\_svr | 90% | 0.8-1.0 | (REF) |

The APK-AV software simulates enrollment of PWID into anti-HCV antiviral treatment. All enrollments will be at a rate of **enrollment\_rate** per 1000 per year.[[5]](#footnote-6) Multiple enrollment methods are supported, and they are expected to lead to different outcomes in the long term.

APK will first identify all eligible individuals, and secondly they will enter treatment at a daily rate corresponding to the annual enrollment\_rate.

Enrollment is assumed to begin January 1, 2016.

*Explanation of recruitment methods*

* Unbiased: selects HCV+ individuals at random.
* HRP: random selection, but only for those who already registered in one of the harm reduction programs (HRPs).
* Fullnetwork: selects a random HCV+ PWID individual and recruits all members of their network who are also HCV+. This provides treats the entire network, and is similar to Hellard et al.[[6]](#footnote-7) .
* Inpartner: a practical methods based on an insight on network theory to find individuals who endanger others. A random PWID is selected (“ego”). If the ego is HCV+, then the ego is treated. Ego is asked to name all persons who give syringes to ego (“alters”). These alters are tested for HCV, and a single HCV+ alter, if any exists, is enrolled.
* Outpartner: similar to “inpartner” but the alter is any person *receiving* (rather than giving) syringes from the selected ego. This finds individuals who are at high risk from ego.
* [optional extension – not completed] Only individuals who are in F4 stage of fibrosis or beyond, based on recent guidelines from insurance companies and CMS (TODO: references)

We will examine the effectiveness of these strategies individually, and also combinations of the strategies.

**Treatment structure**

The duration of treatment will be 12 weeks by default, based on recent all-oral AV (parameter **treatment\_duration**).

Treated individuals will be assigned into one of three groups.

1. SVR group (proportion given by parameter **treatment\_svr**) who will see rapid drop in viral titers followed by viral clearance.
2. Non-SVR. The individual adhers to the treatment but does not achieve SVR. Viral load rebounds after the end of treatment and they become infectious.
3. Non-adherent.

Because of lower adherence, treatment\_svr parameter will be lower than for the general population. Therefore, we will subdivide both group 1 and group 2 into adherent and non-adherent. If non-adherent, a PWID will suppress viral titers below infectious levels during the treatment period but would ultimately develop chronic HCV infection.

During treatment, individuals will remain infectious for a **mean\_days\_residual\_hcv\_infectivity**. Breakout infections will be infrequent and assumed not lead to new infections. Individuals in treatment may become exposed to new infections but, because of the antivirals in their bloodstream, the infection has a negligeably low probability of being established.

Individuals who obtain SVR will be assigned into a cured state, a new state as compared to the original APK software. In subsequent HCV exposures, the software would allow them to become re-infected and possibly progress to HCV. Cured individuals remain at risk for HCV if re-exposed but the risk is not well-established in the literature. We will explore this using sensitivity analysis by using the parameter **treated\_susceptibility.** This parameter is the relative probability of clearing a secondary infection, as compared to naïve individuals. By default, it is set to 1.0, i.e. the susceptibility among cured is equal to susceptibility of naïve PWID.

An individual who previously cleared an infection spontaneously is generally more likely to recover sponteneously in the future. In APK, this history is taken into account and the individual remains more resistant to reinfections in the future, even after possibly receiving AV treatment. Thus AV treatment does not diminish adapted antibodies.

Because of cost considerations, individuals in the US are not generally allowed to repeat AV treatment if they fail the first attempt. [[7]](#footnote-8)

(parameter **treatment\_repeatable**).

**Statistical analysis**

## **Results**

We compared the reduction in HCV prevalence following different recruitment strategies at a constant treatment rate...

*Figure R1: Reduction in overall HCV prevalence among PWID, based on recruitment methods. Assuming only one method is used. B=baseline at start of recruitment (2015), X=no recruitment, U=Unbiased random recruitment, HRP=Harm reduction programs, FN=Full network, IN=in network, OUT=out network.*

Which scale-up rate (n per 1000 PWID) is necessary to reduce by 50% the prevalence in 10 years?

*Figure R2: Scale-up of treatment needed to halve HCV prevalence under different recruitment regimes*

We examined the probability of receiving treatment by group, and see if the recruitment is equitable

*Figure R3: Impact of enrollment methods on subpopulations of PWID. Highlight inequities.*

*Table R4: Comparison of model results to ODE results.*

**DISCUSSION**

[overall significance of the model]

[discussion of ODE result]

**CONCLUSION**

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**Bibliography**

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**APPENDIX**

1. <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0135901> [↑](#footnote-ref-2)
2. <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0137993> [↑](#footnote-ref-3)
3. Parameter file gives these values. It also has TRIALvalue entries, which should be used for quick debugging. [↑](#footnote-ref-4)
4. See AASLD abstract (which one?) [↑](#footnote-ref-5)
5. Cousien, Tran et al. Hepatology 2015 examined the role of linkage to care and disease progression. Namely, they account for the likelihood of the PWID being tested, as well as being an advanced stage of disease which would receive DAA treatment. In effect, our model of flat recruitment rate (10 per 1000) represents all factors that limit access to care, which includes cost of care, but also other factors. It might be more realistic to separately model them, as do Cousien et al. [↑](#footnote-ref-6)
6. The Impact of Injecting Networks on Hepatitis C Transmission and Treatment in People Who Inject Drugs. HEPATOLOGY 2014;60:1861-1870) [↑](#footnote-ref-7)
7. See e.g. <http://www.hmsa.com/PORTAL/PROVIDER/MM.04.034_Harvoni_(Ledipasvir_Sofosbuvir)_for_Treatment_of_Hepatitis_C_120114.pdf> [↑](#footnote-ref-8)