Re-treatment with direct-acting antivirals policy is needed to eliminate Hepatitis C among persons who inject drugs

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ABSTRACT

Background and Aims Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease and mortality worldwide. Direct-acting antiviral (DAA) therapy leads to high cure rates. However, persons who inject drugs (PWID) are at risk for reinfection after cure and may require DAA retreatment to reach the World Health Organization's (WHO) goal of HCV elimination by 2030. We aim to project the frequency of retreatment and DAA cost needed to achieve WHO goals. **Design** We use an agent-based model (ABM) that accounts for the complex interplay of demographic factors, risk behaviors, social networks, and geographic location for HCV transmission among PWID. **Setting and participants** 32,000 in-silico PWID in metropolitan Chicago. **Intervention and comparator** Possible treatment adherence rates (i.e., DAA cure rates) of 60%-90% with DAA treatment enrollment rates of 2.5%-10% and retreatments per PWID of 0 (retreatment prohibited), 1, 2, 3, or no retreatment restriction were simulated. DAA cost is assumed $25,000 (USD) per treatment. **Findings** Modeling results indicate that prohibition of retreatment in PWID would jeopardize achieving the WHO goal of reducing the incidence of new chronic HCV infections by 90% by 2030. We predict that with a DAA treatment rate of >7.5% per year and high (90%) adherence, 75%, 19%, 5% and <2% of PWID will require 1, 2, 3, and 4 treatment courses with overall DAA cost of $325 million to achieve the WHO goal in metropolitan Chicago. We estimate a 28% increase in the overall DAA cost under low adherence (70%) compared to high adherence (90%). **Conclusions** Modeling results predict the frequency of DAA retreatment needed to achieve the WHO goal and underscore the importance of retreatment of HCV re-infections.

INTRODUCTION

Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease and mortality worldwide. Globally, an estimated 71 million people have chronic HCV infection, with an estimated 2.4 million in the United States [1]. Persons who inject drugs (PWID) are at the highest risk for acquiring and transmitting HCV infection [2]. Approximately 32,000 PWID reside in metropolitan Chicago, Illinois and an estimated 47% are chronically infected with HCV [3]. Access to highly efficacious direct-acting antivirals (DAAs) for PWID will be critical to achieving the World Health Organization's (WHO) goal of reducing new chronic infections by 90% by 2030 [4]. Data from several studies have shown that DAA therapy has not increased injection risk behaviors among PWID [5-7]. Nonetheless, high uptake of DAA is expected to paradoxically increase HCV incidence initially even with stable or decreased risk behaviors due to a temporary increase in the pool of PWID susceptible to reinfection [8]. As such, the effectiveness of treatment strategies on incidence should consider the impact of reinfection in PWID [9], particularly among those whose drug use often spans decades [10].

Mathematical modeling can provide insights into strategies that may help to achieve HCV elimination among PWID. A recent review on mathematical modeling of HCV elimination in PWID by Pitcher et al [11] identified more than 60 papers on the subject. In several studies, retreatment was prohibited in PWID who failed to reach cure after DAA therapy [12, 13]. In particular, while Scott et al. [14] emphasized the importance of retreatment, none of the previous modeling studies were designed to predict in detail the frequency of retreatment, the impact of retreatment on DAA cost, or the effect of treatment adherence on achieving the WHO goal.

Model-based examinations of the effectiveness of DAAs on reducing new chronic HCV infections among PWID that account for the complex interplay of demographic factors, risk behaviors, social networks, and geographic location are needed to inform development of effective elimination strategies [15]. Using a detailed agent-based modeling (ABM) approach, we examined the effectiveness of DAA

treatment at four (2.5%, 5%, 7.5%, 10%) enrollment rates on achieving the WHO's incidence reduction goal. Specific consideration was given to the impact of the prohibition of retreatment on new chronic infections after achieving cure as well as the retreatment of those who did not achieve SVR, at different treatment adherence rates (60%-90%).

METHODS

HepCEP model overview

In the present study, we extended our previous work on simulating the PWID population in metropolitan Chicago, Illinois, USA, including the social interactions that result in HCV infection [16, 17]. We adapted the Hepatitis C Elimination in PWID (HepCEP) model to identify DAA therapy rates and treatment strategies for achieving the WHO's goals of reducing new chronic infections by 90% by the year 2030 [17]. The demographic, behavioral and social characteristics of the *in silico* PWID population is generated using data from multiple empirical studies on Chicago area PWID and includes for each individual: age, age of initiation into injection drug use, gender, race/ethnicity, zip code of residence, HCV infection status, drug sharing network degree, parameters for daily injection and syringe-sharing rates, and harm reduction/syringe service program (SSP) enrollment [16]. PWID agents may leave the population due to age-dependent death or drug use cessation and are replaced with new PWIDs sampled from the input data set to maintain a nearly constant population size of 32,000 for the entire course of the simulation.

Network formation

Syringe-sharing is modeled as the primary mode of HCV transmission among PWID who, in HepCEP, are connected via syringe-sharing networks. Network formation is determined by the probability of two persons encountering each other in their neighborhood of residence, within the drug market areas in

Chicago, Illinois that attracts both urban and non-urban PWID for drug purchasing and utilization of SSPs that are also located in the same areas [18]. The methods used to calculate network encounter rates, establishment processes, and removal of networks are detailed in [16]. Each individual has a predetermined number of in-network PWID partners who give syringes to the individual and out-network PWID partners who receive syringes from the individual. The network edge direction determines the flow of HCV-contaminated syringes between individuals, and thus the direction of HCV transmission. The network is dynamic, and during the course of simulation some ties may be lost, while new ties form, resulting in an approximately constant network size.

DAA Treatment Enrollment

Treatment enrollment is modelled as (unbiased) random sampling of chronically infected PWID. The annual target enrollment rate, defined as the total annual treatment enrollment as a fraction of the total population, is a model parameter with range of 1-10%. We model a treatment duration of 12 weeks. DAA treatment success probability is a function of the treatment adherence and SVR parameters. While recent reported SVR rates are close to 99% [19-21], we use a conservative estimate for SVR rates for PWID of 90%. The treatment adherence parameter is varied between 60%-90% to encompass the combined effects of behavioral, drug use and social factors that affect treatment completion (e.g., lost to follow-up, missed doses, enrollment in medication-assisted therapy) reported in the literature [22-25]. Treatment re-enrollment(s) is allowed for PWID who have completed a successful treatment and became re-infected. We assume that successful treatments do not affect the probability of subsequent re-infections [8]. The total PWID target enrollment for a single day is determined by the daily mean treatment enrollment, which is the total PWID population multiplied by the annual treatment enrollment parameter / 365. The daily enrollment target is sampled from a Poisson distribution using the daily mean treatment enrollment. DAA cost is assumed $25,000 (USD) per treatment [26].

Retreatment Restriction and Prohibition

To examine the impact of restricting the number of allowed DAA retreatments per PWID, we conducted a series of 80 unique numerical experiments to account for different enrollment rates (2.5%, 5%, 7.5%, 10%), treatment adherence (60%, 70%, 80%, 90%) and number of allowed DAA retreatments (0, 1, 2, 3) with 20 stochastic replicates each, for a total of 1,600 simulation runs; the choice of allowing up to three retreatments (in response to four separate infections) per PWID provides an opportunity to examine a retreatment policy that reflects reinfection frequency among PWID reported in published studies [9]. Although in clinical practice the number of DAA retreatments per PWID may be limited, we also examined a scenario that does not impose re-treatment restrictions among those with reinfection and/or failed SVR designed to show the value of unconstrained retreatment policy on incidence.

Simulations were conducted using high-performance computing workflows implemented with the EMEWS framework [27]. The simulation experiments were executed on the Bebop cluster run by the Laboratory Computing Resource Center at Argonne National Laboratory. Each simulation requires approximately one hour of wall time to complete. Using the EMEWS workflow on the Bebop cluster, the actual compute time is also one hour since all runs can execute in parallel on 1,600 processes.

ABM Simulation Timeframe

The ABM simulation start date of 2010 was selected based on the PWID demographic data from multiple surveys in previous years [16]. 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 annual incidence of chronic HCV relative to the mean baseline incidence rate in year 2020 with no treatment (enrollment rate of 0%). Each individual model PWID agent steps through their current activity on each simulation day and transitioning between activities is dependent on the agent's current state (e.g. infected) and the scheduled duration of each activity.

Figure 1 shows an example of the activity timeline for a single PWID agent during model simulation, beginning with the agent's first DAA treatment, and highlights the detail and discrete nature of the model. The example timeline is produced from a real simulation event log in which the number of retreatments is limited to three (i.e. total of 4 treatment courses). The frequency and timing of reinfection events is consistent with those reported in the literature for PWID [9]. The agent is enrolled in DAA treatment in mid-2020 and successfully completes treatment. For several months between late 2020 and early 2021, the agent is cured (SVR), but is re-infected and soon after is enrolled in DAA treatment which is successful, and the agent remains cured until early 2022. The agent is re-infected and recruited for DAA treatment, which is unsuccessful, causing the PWID to remain in the infected state until early 2023, at which time the PWID is enrolled in DAA treatment and cured again. The PWID is re-infected again in early 2024 and remains in the infected state until the end of the simulation as the retreatment threshold of three re-treatments has been exceeded. In the HepCEP model, individual PWID agent treatment can be customized on an individual level, allowing for treatment approaches and constraints to be uniquely set for each person.

Annual Incidence Determination

The mean annual relative incidence is defined as

$$Annual\ Incidence\ Rate = \sum_{i=1}^{365} \frac{new\ chronic\ infections\ daily_i}{population_i - infected_i}$$

where *i* represents the day of the year. The denominator represents the total number of individuals that are eligible to become infected, while the numerator is simply the number of daily incident chronic infections. This formulation assumes that treated individuals can be re-infected after SVR and that re-infected individuals are treated as new infections, which is included in the numerator of infected daily.

The mean annual incidence rate and 95% confidence interval per DAA enrollment grouping is determined from the 20 stochastic runs.

RESULTS

Model predicts that WHO goal will not be reached with retreatment restriction

Figure 2 depicts chronic infection incidence for the four DAA-therapy enrollment rates with retreatment prohibition and a treatment adherence of 90%. Due to the increase in availability of newly-cured, susceptible PWID who can re-acquire HCV, there is a projected increase in incidence during the first 1-3 years after DAA therapy initiation, followed by a transient decline, then convergence to half of the incidence prior to DAA therapy initiation. This pattern does not achieve the WHO goal by year 2030, not even with DAA enrollment rates of up to 10% and an optimistic treatment adherence of 90% (Figure 2). Since the WHO goal could not be achieved even with a 90% treatment adherence under retreatment prohibition, no further simulations utilizing lower treatment adherence rates were conducted.

Model predicts that WHO goal will be reached without retreatment restriction

With retreatment restriction removed, multiple scenarios were simulated in which both the DAA-therapy enrollment rate and the treatment adherence are varied. DAA enrollment rates of ≤5% are not effective in achieving the WHO goal by 2030 with treatment adherence <80% (Figure 3A, 3B). We found that an enrollment rate of ≥5% with a treatment adherence threshold of ≥80% can both achieve the WHO target of 90% incidence reduction (Figure 3C, 3D); as such, an enrollment rate of 7.5% has been identified as the conservative lowest enrollment rate for which the WHO goal can be achieved by 2030 for this group (Figure 3). Overall, a DAA enrollment rate of 7.5% with a treatment adherence of 90% would achieve the WHO goal the earliest (year 2026; Figure 3D), with treatment adherence of 60% still meeting the goal by 2029 (Figure 3A). The effects of adherence impact the speed at which the WHO goal is met to a lesser

degree for a treatment enrollment rate of 10%, i.e., 90% and 60% adherence result in reaching the goal by 2025 and 2027, respectively (Figure 3D, 3A).

The HCV incidence rate reduction predicted by the model clearly demonstrates that the WHO goal is achievable by year 2030 when retreatment is not prohibited (Figure 3). However, while each PWID could potentially be retreated without restriction in the model in this scenario, we show that only a small proportion of PWID require more than three retreatments for the duration of the simulation, e.g. 2% for DAA enrollment rates ≥7.5% and adherence rates >60% (Table 1).

Model predicts WHO goal will be reached with DAA therapy rates of ≥7.5% when limiting therapy to up to 3 retreatments per PWID.

Figure 4 shows the incidence of new chronic HCV infections when only a single retreatment is allowed for each PWID. The incidence curves in Figure 4 are qualitatively similar to those for the no retreatment restriction scenario (Figure 3) such that the rate of incidence reduction is proportional to the DAA enrollment rate. However, the single retreatment scenario model predicts that the lower bound on incidence is constrained by the single retreatment policy, independent of the enrollment rate, even for adherence of 90% (Figure 4D), and the WHO goal cannot be achieved.

When the number of retreatments per PWID is increased to two retreatments (three treatments total), the WHO incidence reduction goal is achievable by year 2030 for DAA enrollment rates ≥ 7.5% and adherence ≥ 80% (Figure 5C, 5D). As in the single retreatment scenario, the two-retreatment scenario exhibits a lower limit on incidence reduction, although the limit approaches close to zero for high treatment adherence rates (≥90%). When up to three retreatments (four total treatments) per PWID are allowed, the incidence reduction goal is achieved for DAA enrollment rates ≥ 7.5% and adherence ≥ 60%, similar to the no retreatment restriction scenario. The similarity in incidence reduction between the no retreatment restriction and the three-retreatment scenarios is reflected by the fact that a very small

fraction (<2%) of PWID require more than three retreatments in the no retreatment restriction scenario, suggesting that limiting the number of retreatments per PWID to three retreatments total is sufficient to achieve the WHO goal by 2030.

Table 2 provides a summary of the retreatment frequency for PWID in the two and three retreatment limit scenarios for low (70%) and high (90%) treatment adherence rates with a DAA enrollment rate of 7.5%. In the case of high adherence and a 90% DAA cure rate, the model predicts that 75% of PWID will require no retreatment (i.e., a single treatment), 19% will require one retreatment, 5% will require two retreatments, and <2% of PWID will be require three retreatments with DAA treatment rates of ≥ 7.5% per year. With the cost of $25,000 per course of DAA treatment, the overall DAA cost to achieve the WHO goal among PWID in metropolitan Chicago with high adherence when up to three retreatments are allowed is approximately $325.3 million (95% CI: 323.6-327.2, Table 3), and nearly the same for when up to two retreatments are allowed ($326.4 million, 95%CI: 324.3-328.6, Table 3). For scenarios with low (70%) adherence, the model predicts that more DAA treatment courses (9859, 95% CI: 9821-9897, Table 2) are needed to achieve the WHO goal when three retreatments are allowed at an increased cost compared to the high adherence (90%) scenario (9778, 95% CI: 9738-9818), Table 2). The cause of this difference is evident by the percentage of PWID receiving 0, 1, 2, and 3 retreatments in Table 2. The high versus low adherence scenario results in 75% vs. 58% of PWID requiring only a single treatment. Since the treatment failure rate is higher in the low adherence scenario, a disproportionate number of PWID need to reenroll in DAA treatment 2-3 times compared to the high adherence scenario. The model estimates a 28% increase in total DAA cost under low adherence ($417.0 million, 95% CI: 414.6-419.4, Table 3) compared to the high adherence scenario ($325.3 million, 95% CI: 323.6-327.2, Table 3).

DISCUSSION

Our PWID model simulations underscore the importance of DAA therapy that includes retreatment of re-infected individuals in order to achieve significant reductions in chronic HCV infection incidence.

Retreatment, which has been shown to reduce/eradicate viral titers multiple times for the same person (Figure 1), is predicted to be highly efficacious to curtail transmission (i.e., reducing incidence). An unbiased DAA enrollment rate of 7.5% (75 per 1000 PWID) per year is projected to achieve the WHO target of 90% incidence reduction by 2030, if retreatment is provided up to 3 times (i.e., a total of 4 treatment courses), even with treatment adherence rates as low as 60% (Figure 6).

Total program treatment costs for the scenario with 7.5% DAA treatment enrollment and 90% adherence are larger when treatment prohibition is removed compared to the scenario with treatment prohibition (Table 4). When retreatment is disallowed, the total costs during the treatment enrollment period years 2020-2030 is $258.2 million (95% CI: 257.3-259.0), compared with a total cost of $325.3 million (95% CI: 323.6-327.2), for up to three allowed retreatments (Table 4). However, as has been shown, limiting retreatments will not achieve the WHO goal for reducing new chronic infections by year 2030, unless more than two retreatments per PWID is allowed (Figures 2-6). Total treatment costs between the scenarios that allow two retreatments ($326.4 million, 95%CI: 324.3-328.6, Table 4) and three retreatments ($325.3 million, 95% CI: 323.6-327.2, Table 4) are nearly identical. The counter-intuitive higher mean total cost in the two-retreatment scenario compared with the three-retreatment scenario can be partly attributed to stochastic variation in the model results, as the 95% CI for total cost overlap. However, perhaps more importantly, Table 4 shows that the total number of infections during the DAA treatment enrollment period from years 2020-2030 actually decrease as the number of allowed retreatments is increased. Limiting DAA retreatment results in a larger pool of infected individuals that may infect other HCV-naïve PWID in their syringe-sharing network. Newly infected individuals subsequently are enrolled in DAA treatment, incurring additional costs even though the PWID who is the source of the infection is unable to re-enroll due to retreatment limitations.

Our modeling results have important public health implications for HCV elimination among U.S. PWID. Using a range of feasible treatment enrollment and adherence rates, we report robust findings supporting the need to address re-exposure and reinfection among PWID to reduce HCV incidence. Our ABM approach allows us to model PWID at the individual level and examine the effects of social network interactions on needle sharing and HCV transmission, as well as to examine how treatment enrollments target specific individuals. In our recent ordinary differential equation (ODE) model study [28], we predicted that a DAA-treatment rate of 6.4% (with no retreatment restriction) with an SVR rate of 90%, would be needed to reach the WHO elimination goal of 90% reduction of incidence over a 10-year treatment period (2020-2030) with a total projected DAA cost of $418 million. This compares to a 7.5% DAA-treatment rate using the HepCEP ABM with a lower DAA cost of $325 million (Figure 6 and Table 2), which would reach the 2030 reduction in chronic infection incidence goal. The ODE approach does not represent the network structure or spatial and demographic heterogeneity of the PWID population that modulate the transmission risk and, therefore, results in an overestimate of the actual cost needed to reach >90% reduction. As such, our ABM is more suitable than ODE modeling for predicting the effects of any barriers to treatment.

Our study has several limitations. First, the model conservatively included both reinfection and unsuccessful treatment (failure to achieve SVR) in the retreatment prohibition scenario (Figure 2), which effectively inflates the number of retreatments needed to meet the WHO incidence goal elimination relative to considering only retreatment for reinfection. However, the WHO goal still cannot be achieved with an enrollment rate of 10% with retreatment prohibition, underscoring that retreatment of HCV re-infections is needed to achieve the desired reduction in incidence by 2030. Second, our model also assumes that PWID's underlying risky behaviors remain constant, but patterns of drug use and injection behaviors may change following DAA treatment [29]. Third, while we account for enrollment in SSPs, we did not evaluate the impact of retreatment in combination with also scaling up harm reduction services.

A recent meta-analysis of 36 studies, which showed the highest risk of reinfection after successful treatment among people with recent drug use not receiving opioid-agonist therapy (6.6 per 100-years), highlights the importance of targeting this group for concurrent medication-assisted drug use therapies [30] and risk reduction strategies (e.g., access to harm reduction, DAA treatment of injection network members) in addition to retreatment if needed. Fourth, linkage to care (or enrollment) to DAA treatment was assigned in HepCEP randomly without considering the time to screen and linkage to care PWID to DAA treatment. Fifth, PWID co-infected with HCV and HIV were not modeled in HepCEP. Data from a large SSP in metropolitan Chicago [31] that attracts both urban and suburban PWID show that from 2011 to 2016 3.2% were HIV positive, 21% were HCV positive, and 2.3% were HIV/HCV co-infected. Evidence over the past decades have shown that HIV/HCV coinfected patients did not respond as well to HCV therapy as HCV mono-infected patients. However, with the advent of DAA therapy for HCV, treatment efficacy now appears comparable for HIV/HCV coinfected and HCV mono-infected patients [32-34]. As such, we do not expect HIV/HCV co-infected participants to have a major effect on the current ABM predictions.

A recent study suggests that the United States is not on track to meet the WHO goals for HCV elimination by 2030 [35]. In particular, the Chicago metropolitan area in Illinois is predicted to achieve WHO goals between 2041-2049 and might be further delayed by COVID-19 pandemic [36]. Our study highlights the role of DAA retreatment, its frequency and the importance of treatment adherence needed to achieve the WHO goal in high-risk populations.

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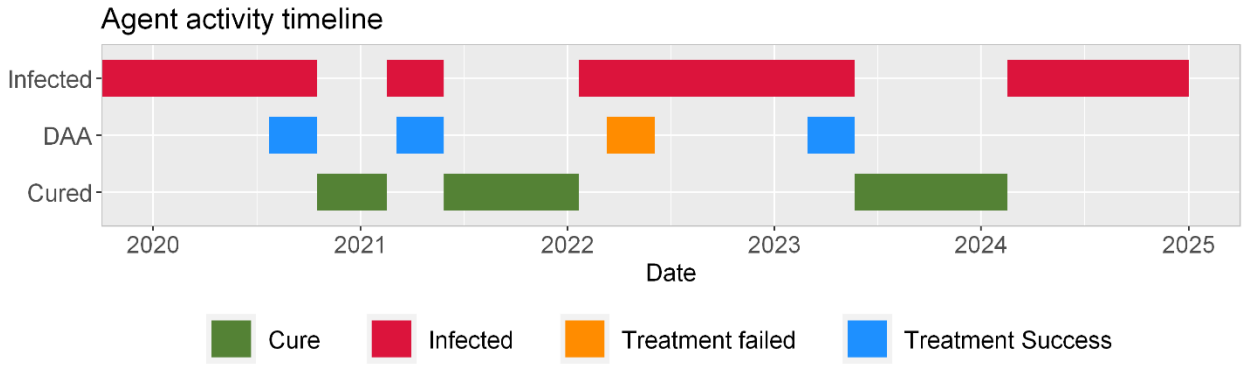

Figure 1. Activity timeline for a single agent in the HepCEP model who was allowed only 4 courses of DAA therapy. The colored bars indicate activities in which the agent is participating during the dates along the bottom of the timeline. The activity pattern shown in the figure are typical in some of HCV-positive agents that are selected for DAA treatment, cured, and re-infected multiple times. In this example, the agent was allowed to re-enroll in DAA treatment 3 times (total of 4 treatment courses), had a single occurrence of failed DAA treatment in year 2022 (orange bar) and eventually was re-infected ~1 year after SVR (in 2024) and remained chronically infected until 2030 (not shown).

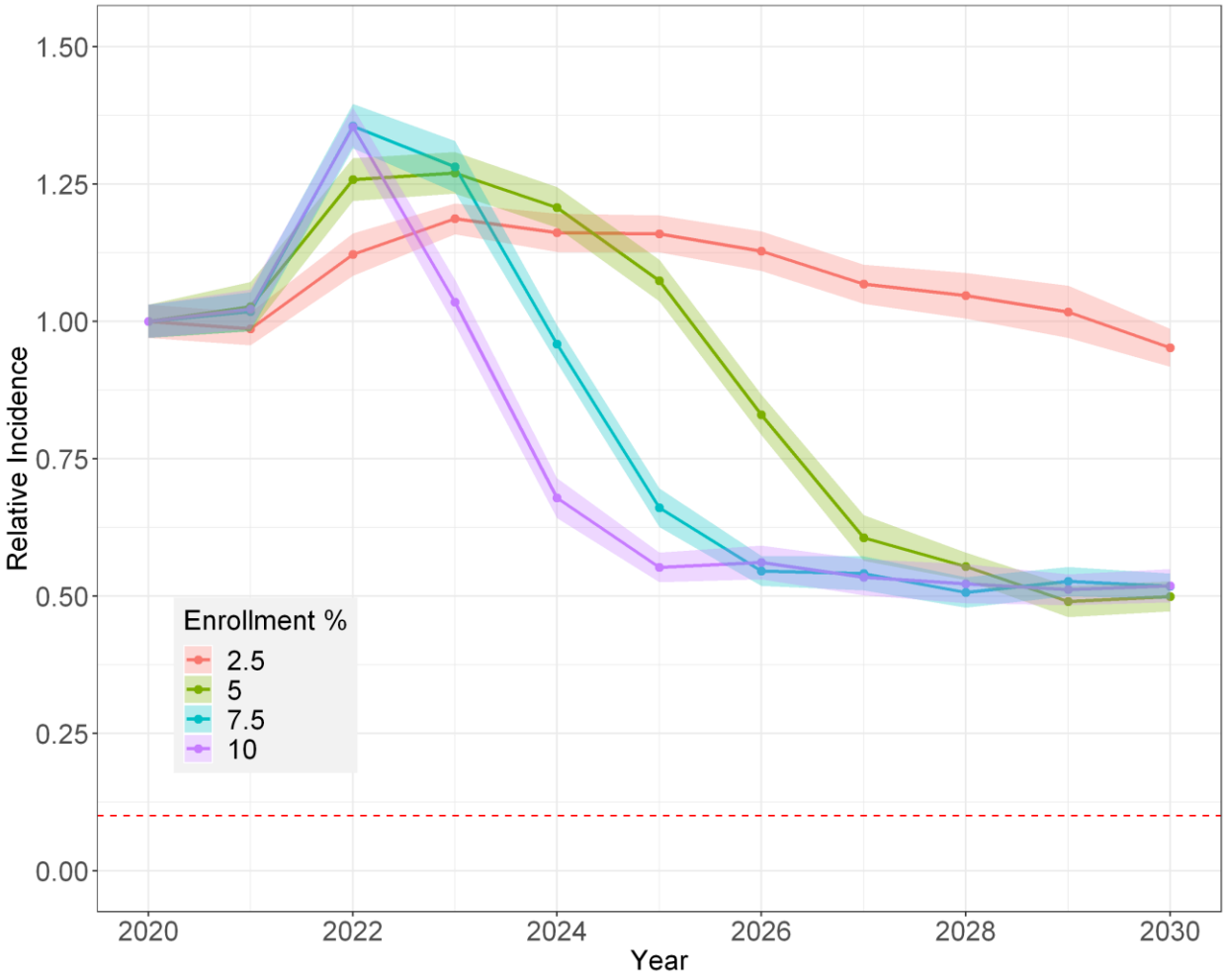

Figure 2. Projected mean incidence of new HCV chronic infections among PWID relative to the predicted 2020 incidence during DAA rate (enrollment percent is DAA rate e.g., a therapy rate of 10% (or 100 per 1000 PWID) per year), with retreatment prohibition and a treatment adherence of 90%. The ribbons represent the 95% confidence interval around the mean of 20 simulation runs. The horizontal red dashed line represents the WHO 2030 goal of 90% reduction in the incidence rate.

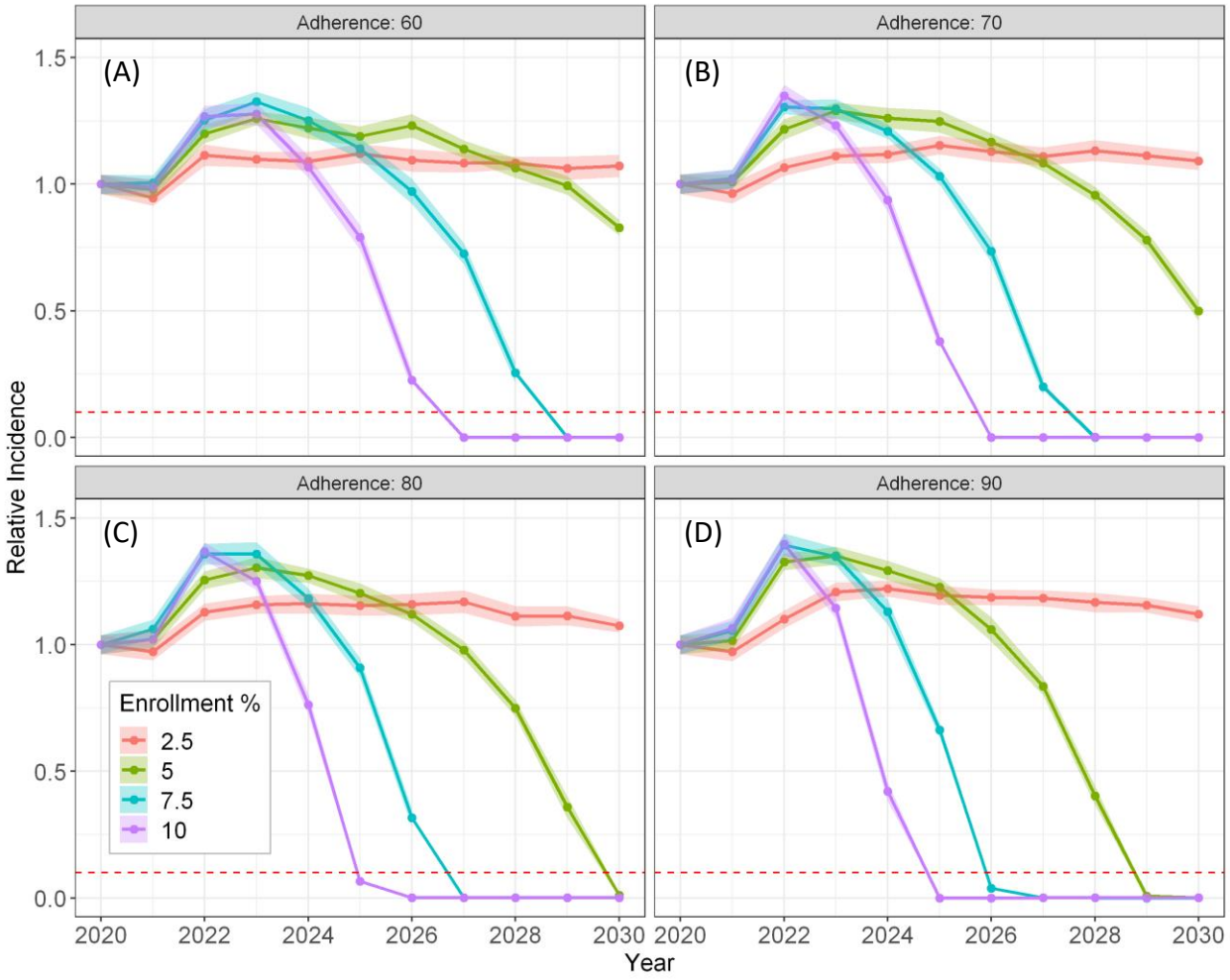

Figure 3. Projected HCV mean incidence of new chronic infections among PWID relative to the predicted 2020 incidence during DAA rate (enrollment percent is DAA rate e.g., a therapy rate of 10% (or 100 per 1000 PWID) per year), without retreatment prohibition and treatment adherence of 60%-90%. The ribbons represent the 95% confidence interval around the mean of 20 simulation runs. The horizontal red dashed line represents the WHO 2030 goal of 90% reduction in the incidence rate.

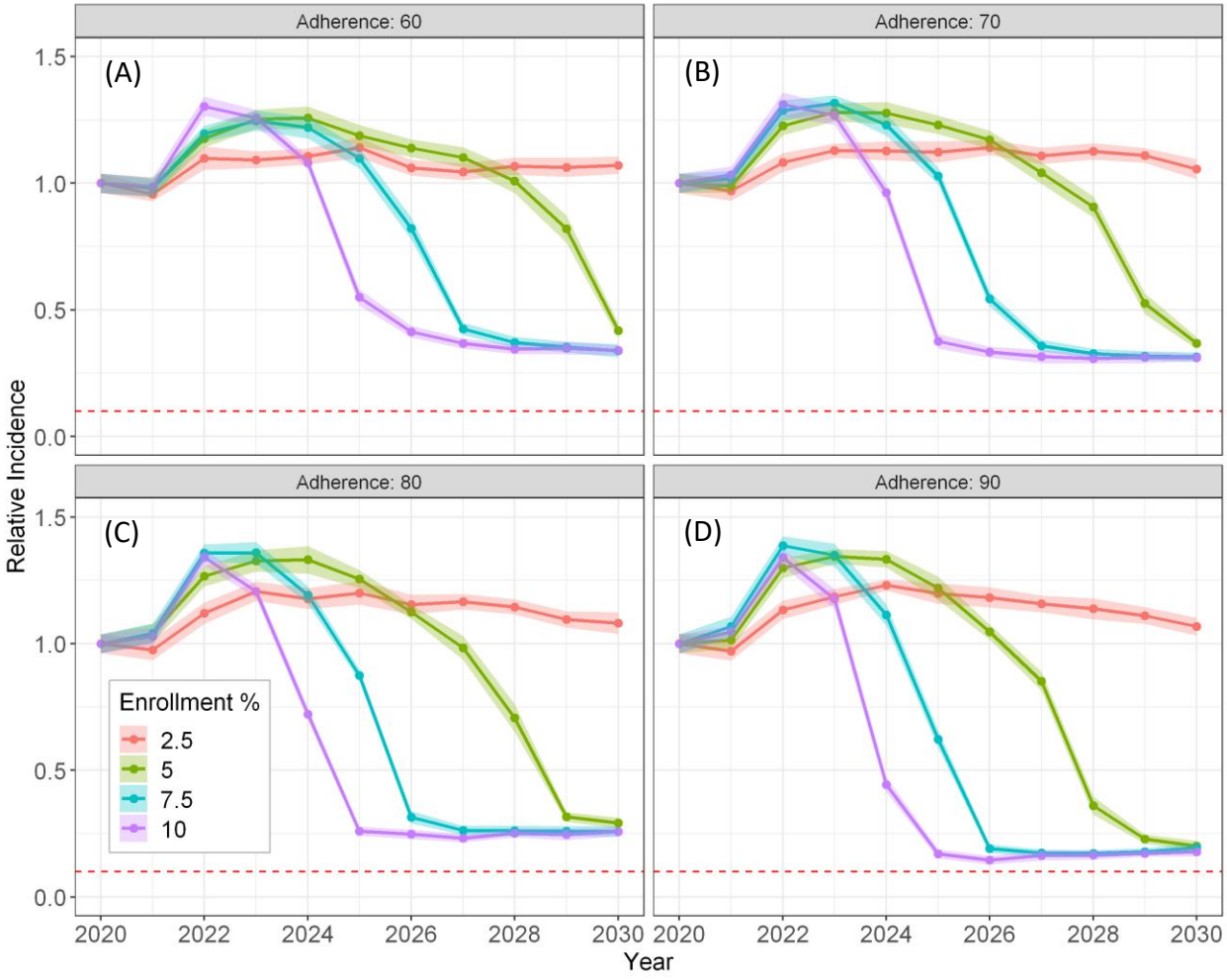

Figure 4. Projected HCV mean incidence of new chronic infections among PWID relative to the predicted 2020 incidence for one allowed DAA retreatment (total treatments = 2), and treatment adherence of (A) 60%, (B) 70%, (C) 80% and (D) 90%. The ribbons represent the 95% confidence interval around the mean of 20 simulation runs. The horizontal red dashed line represents the WHO 2030 goal of 90% reduction in the incidence rate.

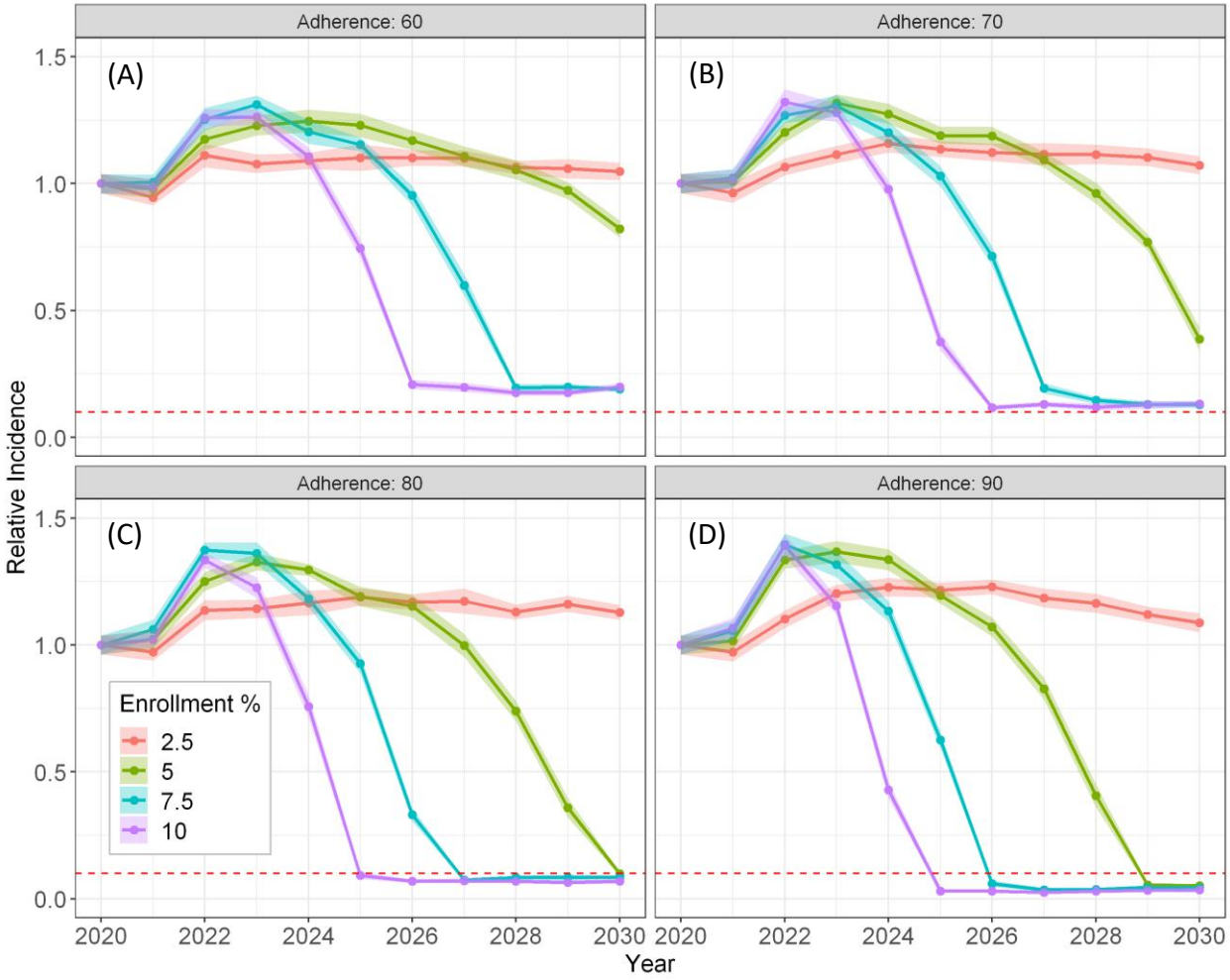

Figure 5. Projected HCV mean incidence of new chronic infections among PWID relative to the predicted 2020 incidence for two allowed DAA retreatment (total treatments = 3), and treatment adherence of (A) 60%, (B) 70%, (C) 80% and (D) 90%. The ribbons represent the 95% confidence interval around the mean of 20 simulation runs. The horizontal red dashed line represents the WHO 2030 goal of 90% reduction in the incidence rate.

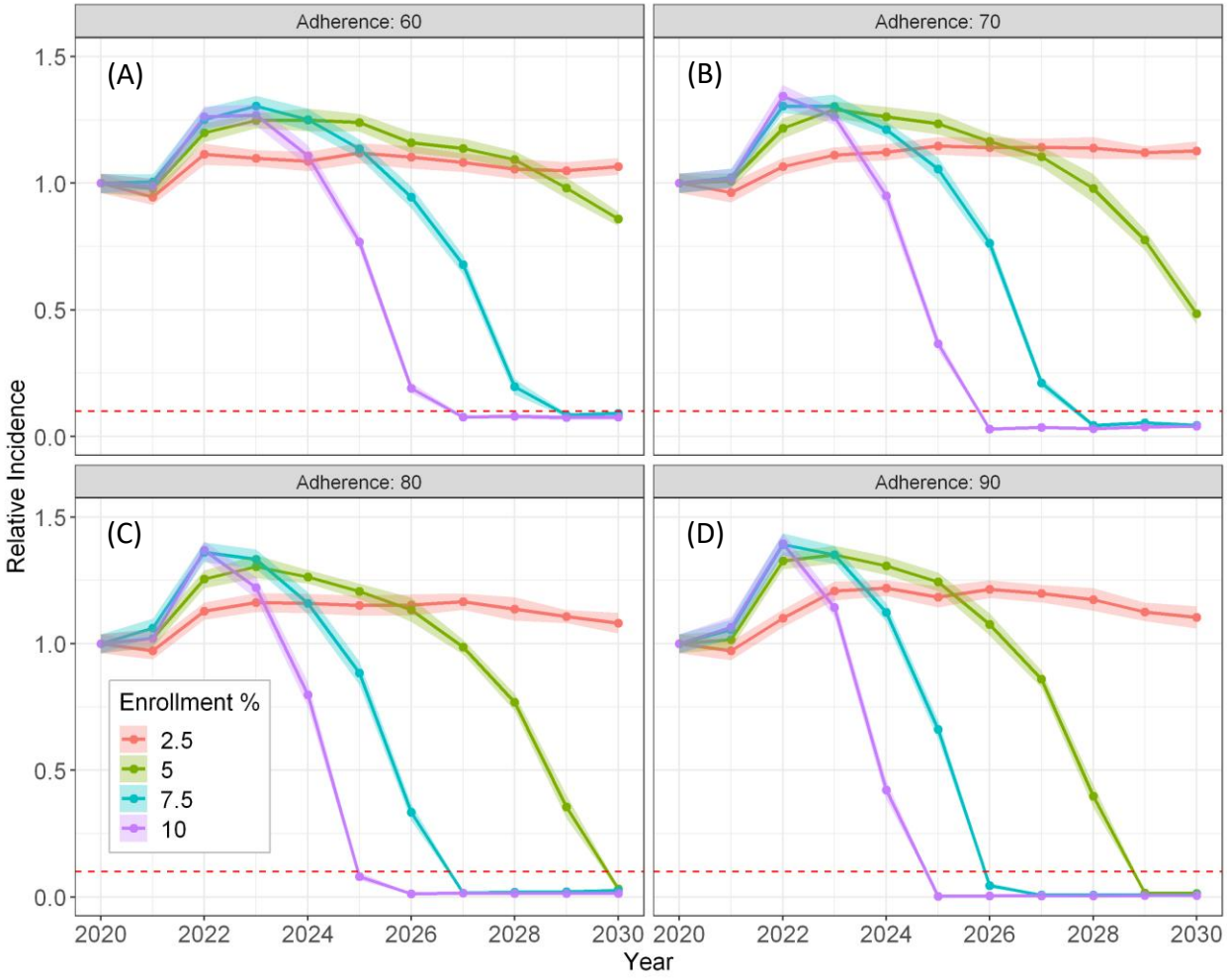

Figure 6. Projected HCV mean incidence of new chronic infections among PWID relative to the predicted 2020 incidence for three allowed DAA retreatment (total treatments = 4), and treatment adherence of (A) 60%, (B) 70%, (C) 80% and (D) 90%. The ribbons represent the 95% confidence interval around the mean of 20 simulation runs. The horizontal red dashed line represents the WHO 2030 goal of 90% reduction in the incidence rate.

Table 1. Mean PWID treatment enrollment frequency and DAA costs (95% CI) for DAA treatment rate of 7.5% per year when unlimited retreatment is allowed, and treatment adherence (TA) of 90% (A) and 70% (B). Number treated values are rounded to the nearest integer. Percent treated is the fraction of PWID treated by number of times in each row relative to the total number of all individual PWID treated. DAA cost per treatment is $25,000.

(A) TA 90%

Times Retreated	Number of PWID Treated		Percent	Cost [1K $]	
0	7368	(7330 - 7406)	75.4	184,201	(183,254 - 185,148)
1	1805	(1785 - 1826)	18.5	90,273	(89,254 - 91,291)
2	461	(447 - 476)	4.7	34,586	(33,505 - 35,668)
3	108	(104 - 113)	1.1	10,825	(10,365 - 11,285)
4	28	(25 - 30)	0.3	3,450	(3,088 - 3,812)
5	5	(4 - 6)	0.1	803	(630 - 975)
6	1	(1 - 2)	< 0.1	256	(186 - 326)
7	1	(-)	< 0.1	229	(159 - 298)
8	1	(-)	< 0.1	225	(-)
Total:	**9777**	**(9739 - 9816)**	**100.0**	**324,395**	**(322,785 - 326,005)**

(B) TA 70%

Times Retreated	Number of PWID Treated		Percent	Cost [1K $]	
0	5773	(5707 - 5761)	58.5	143,324	(142,634 - 144,014)
1	2382	(2362 - 2403)	24.3	119,123	(118,095 - 120,149)
2	1005	(988 - 1023)	10.3	75,401	(74,084 - 76,718)

3	413	(402 - 424)	4.2	41,330	(40,238 - 42,422)
4	162	(154 - 170)	1.7	20,275	(19,254 - 21,296)
5	64	(60 - 68)	0.6	9,555	(8,984 - 10,126)
6	26	(23 - 29)	0.3	4,568	(4,091 - 5,044)
7	10	(8 - 11)	0.1	1,920	(1,639 - 2,201)
8	4	(3 - 4)	< 0.1	844	(677 - 1,011)
9	2	(1 - 2)	< 0.1	417	(282 - 552)
10	1	(0 - 2)	< 0.1	367	(131 - 602)
11	1	(-)	< 0.1	300	(-)
12	1	(-)	< 0.1	325	(-)
Total:	**9,801**	**(9761 - 9841)**	**100.0**	**416,840**	**(414,371 - 419,309)**

Table 2. Mean PWID treatment enrollment frequency (95% CI) for DAA treatment rate of 7.5% per year when retreatment is allowed up to two and three times, and treatment adherence (TA) of 90% (A) and 70% (B). Number treated values are rounded to the nearest integer. Percent treated is the fraction of PWID treated by number of times in each row relative to the total number of all individual PWID treated. The related DAA cost is shown in Table 3. *Indicates scenario does not achieve WHO incidence elimination goal.

(A) TA 90%

	Allowed Retreatments: 2			Allowed Retreatments: 3		
Times Retreated	Number of PWID Treated		Percent	Number of PWID Treated		Percent
0	7291	(7257 - 7325)	74.3	7338	(7303 - 7374)	75.1
1	1808	(1788 - 1828)	18.4	1810	(1787 - 1833)	18.5
2	717	(694 - 740)	7.3	465	(454 - 475)	4.8
3				165	(157 - 173)	1.7
Total:	**9816**	**(9773 - 9860)**	**100.0**	**9,778**	**(9738 - 9818)**	**100.0**

(B) TA 70%

	Allowed Retreatments: 2*			Allowed Retreatments: 3		
Times Retreated	Number of PWID Treated		Percent	Number of PWID Treated		Percent
0	5577	(5547 - 5607)	56.2	5668	(5641 - 5694)	57.5
1	2340	(2320 - 2360)	23.6	2371	(2354 - 2388)	24.0
2	2003	(1972 - 2033)	20.2	1009	(997 - 1022)	10.2
3				811	(789 - 833)	8.2
Total:	**9,920**	**(9875 - 9965)**	**100.0**	**9,859**	**(9821 - 9897)**	**100.0**

Table 3. Mean treatment costs (95% CI) for DAA treatment rate of 7.5% per year when retreatment is allowed up to two and three times, and treatment adherence (TA) of 90% (A) and 70% (B). Cost values are rounded to the nearest 1K$. The DAA cost per treatment is $25,000. The related number of treatments is shown in Table 2. Treatment costs for each group (times retreated) is calculated as the number treated in each group multiplied by the number of times treated multiplied by the cost per treatment. *Indicates scenario does not achieve WHO incidence elimination goal.

(A) TA 90%

	Allowed Retreatments: 2		Allowed Retreatments: 3	
Times Retreated	Cost [1K $]		Cost [1K $]	
0	182,278	(181,435 - 183,120)	183,458	(182,569 - 184,346)
1	90,395	(89,399 - 91,391)	90,485	(89,336 - 91,634)
2	53,790	(52,084 - 55,496)	34,845	(34,028 - 35,662)
3			16,520	(15,710 - 17,30)
Total:	**326,463**	**(324,313 - 328,612)**	**325,308**	**(323,381 - 327,234)**

(B) TA 70%

	Allowed Retreatments: 2*		Allowed Retreatments: 3	
Times Retreated	Cost [1K $]		Cost [1K $]	
0	139,424	(138,669 - 140,179)	141,693	(141,026 - 142,359)
1	117,015	(116,012 - 118,018)	118,55	(117,704 - 119,401)
2	150,206	(147,923 - 152,490)	75,698	(74,748 - 76,647)
3			81,100	(78,921 - 83,279)
Total	**406,645**	**(404,050 - 409,240)**	**417,043**	**(414,619 - 419,446)**

Table 4. Mean treatment costs, new chronic infections, and chronic reinfections (95% CI) during the treatment period (years 2020-2030) for DAA treatment rate of 7.5% per year and treatment adherence of 90%. The DAA cost per treatment is $25,000. Cost values are rounded to the nearest 1K$ and infections are rounded to the nearest integer.

Allowed Retreatments	Cost [1K $]		Infections		Reinfections	
0	258,181	(257,332 - 259,031)	1725	(1695 - 1756)	92	(87-97)
1	318,556	(316,675 - 320,437)	1282	(1248 - 1316)	158	(150-167)
2	326,463	(324,313 - 328,612)	1096	(1065 - 1127)	112	(106-119)
3	325,308	(323,381 - 327,234)	1067	(1042 - 1092)	97	(90-104)