# Modeling predicts shortening of DAA treatment duration to 5 weeks in individuals with recent or chronic infection with HCV RNA negativity at day 7 on treatment

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## Abstract

Identifying individuals with hepatitis C virus (HCV) infection who could be cured with a shorter duration of direct-acting antivirals (DAA) therapy would support the effort to reach HCV elimination goals. We used HCV kinetics from treated individuals to generate in silico populations with recent and chronic infection. We assessed response-guided treatment (RGT) strategies based on whether HCV RNA was detectable on day 7 and/or day 14 on-treatment. The analysis predicted that treatment duration could be shortened to 5 weeks for people with recent or chronic infection who have undetectable HCV RNA at week 1 of treatment.

## Introduction

The availability of direct acting antivirals (DAAs) with >95% sustained virological response (SVR; cure) provided the basis for the World Health Organization (WHO) to propose the goal of reducing new hepatitis C virus (HCV) infections by 90% and deaths by 65% by 2030 (*1*). Termed ambitious (*2, 3*), this goal has faced several challenges including limited resources, stigma regarding HCV, and the lack of optimization of the cascade of care (*4*). Recent studies have estimated that fewer than 15 countries are on track to meet the WHO goals (*5-7*). This has prompted an update from WHO calling for scaling up of testing and simplifying treatment and monitoring (*8*), with the latter also being identified as a research gap.

To address this gap, we previously showed that an on-treatment monitoring procedure with limited blood samples and viral load quantification at baseline, week 1 and week 2 allowed mathematical modeling to predict time to cure (TTC) accurately in 10 individuals with chronic HCV infection (*9*). Modeling-based RGT requires viral kinetics, which can be a barrier to implementation. Moreover, this approach cannot be applied to the subset of individuals with HCV

infection who reach undetectable viral loads by week 1 of treatment and thus do not have viral kinetics to predict TTC. Further complicating this matter, rich datasets with early viral kinetic data are rarely readily available from clinical trials to test RGT strategies retrospectively.

Here, we developed a simplified RGT framework that does not require modeling with the aim of minimizing duration of therapy to support worldwide HCV elimination goals

## Methods

### *Participants*

We previously gathered early viral kinetic data from 266 people with chronic HCV infection, mostly genotype 1, treated using a variety of DAAs for 8-12 weeks (*10*). This included N=11 treated with sofosbuvir/velpatasvir (SOF/VEL), elbasvir/grazoprevir, sofosbuvir /ledipasvir, N=44 treated with glecaprevir-pibrentasvir (P/G), N=74 treated with sofosbuvir /simeprevir/ribavirin, ledipasvir /daclatasvir/dasabuvir/ombitasvir/paritaprevir, N=26 treated with SOF/ daclatasvir/asunaprevir/beclabuvir, N=68 treated with daclatasvir + asunaprevir and N=54 treated with SOF+ ledipasvir, sofosbuvir + daclatasvir, sofosbuvir + simeprevir. Mean baseline viral load was ~$10^6$ IU/mL in this cohort and detailed viral kinetics facilitated building and training multiscale mathematical models (S**Fig.S1A**). Based on the analysis of the limited dataset, the viral kinetics of the DAA regimens that were included were comparable (**Fig.S2**).

Similarly, we gathered viral kinetic data from two clinical trials that evaluated 4 week (n=23) and 6 week courses (n=30) of P/G for treatment of people with recent HCV infection, mostly genotype 1 (*11, 12*). P/G is approved as an 8-week treatment regimen. After excluding cases with missing viral load measurements and those who did not complete treatment or follow-up, data were available for n=20 and n=28 individuals from 4- and 6-weeks trials, respectively. Mean baseline viral loads was also ~$10^6$ IU/mL in people with recent HCV infection despite a wider range (i.e., ($10^4$, $10^8$) IU/mL) (*9, 13*) compared to people with chronic HCV infection (i.e., ($10^5$, $10^{7.5}$) IU/mL (*13, 14*)).

### *Mathematical Model*

We generated *in silico* populations of people with chronic and recent HCV infection using a well-established multiscale model (*13, 14*) that shares features and distributions with 266 real world people with chronic HCV infection (*10*) and 53 people with recent HCV infection (*11, 12*) (**SFig.1**). Although the biphasic model has been used widely (*9, 10*), we chose a multiscale model because it better describes viral load response on-treatment, including early response under DAA therapy (*13, 14*).

On-treatment viral loads ($V(t)$) in people with chronic HCV infection are given by the analytical solution of a multiscale mathematical model (*13, 14*)

$$\frac{V(t)}{V(0)} = e^{-ct} + (1-\epsilon_s)\frac{c\rho}{N}\left\{\frac{A}{(B-\gamma)\delta(\delta+\gamma-c)}\left(e^{-ct} - e^{-(\delta+\gamma)t}\right) + \frac{1}{B+\delta-c}\left(\frac{N}{\rho} - \frac{A}{(B-\gamma)\delta}\right)\left(e^{-ct} - e^{-(B+\delta)t}\right)\right\} \quad \textbf{(Eq.1)}$$

where $A = (1-\epsilon_\alpha)\alpha$, $B = (1-\epsilon_s)\rho + \kappa\mu$ and $N = \frac{\rho(\alpha+\delta)}{\delta(\rho+\mu+\delta)}$. The parameters $\alpha$, $\mu$ and $\rho$ are the age-dependent rates of vRNA production, degradation and assembly/secretion, respectively. Three different antiviral effects of therapy with DAAs are included in the model, namely, blocking vRNA production (i.e., reducing a by a factor $(1-\epsilon_\alpha)$, reducing assembly/secretion of virus (i.e., reducing $\rho$ by a factor $(1-\epsilon_s)$), and enhancing the rate of vRNA degradation (i.e., increasing $\mu$ by a factor $\kappa$), where $0 \le \epsilon_\alpha \le 1$, $0 \le \epsilon_s \le 1$ and $\kappa \ge 1$. Moreover, $\delta$, $c$, $\gamma$ and $V(0)$ denote infected cells loss rate, clearance rate of virions, decay rate of intracellular replication templates, and pre-treatment viral loads, respectively. Finally, $N$ represents the total number of virions produced by one infected cell over its lifespan.

***Generation of in silico people with chronic HCV infection***

Individuals chronically infected with HCV had frequent HCV RNA measurements in clinical trials (*13, 14*), which facilitated the identification of parameters in the analytical solution of the multiscale model Eq. 1 (*13, 14*). Since early viral kinetics under P/G and SOF/VEL appeared to be comparable to all other DAAs (**SFig.2**) and early kinetics determine TTC, we did not generate and treat viral kinetics of *in silico* cohorts of individuals with chronic HCV infection who received other DAAs differently. All the parameter values are listed below and the procedure to generate *in silico* people with chronic HCV infection follows as:

(i) Fixed parameters were defined as $\delta$ (0.14/day), $\rho$ (8.18/day), c (22.3/day), $\alpha$ (40.0 vRNA/day), and $\mu$ (1.0/day) (*13, 14*).

(ii) Ranges of remaining parameters were then defined as $\kappa$ (1.46-6.7), $\gamma$ (0.1-0.96/day), $\epsilon_s$ (0.13-0.998), $\epsilon_\alpha$ (0.97-0.999) and *V(0)* ($10^5$, $10^{7.5}$) IU/mL (*13, 14*). All parameters are assumed to follow a uniform distribution.

(iii) 100,000 combinations of parameters listed in steps (i) and (ii) were generated. Each parameter combination corresponded to an *in silico* individual with chronic infection. For each parameter combination, viral loads between 0 and 84 days at an interval of 0.1 day were computed using Eq.1.

(iv) Error model following a normal distribution with mean=0 and standard deviation=0.1 was constructed.

(v) Errors from step (iv) were simulated and added to viral loads in step (iii),thus generating 100,000 *in silico* people with chronic HCV infection.

From this larger cohort, several subsets of 10,000 *in silico* people with chronic HCV infection were identified with characteristics namely, (i) viral loads were below the detection limit on day 7, (ii) viral loads were below the detection limit on day 14 (with viral loads at day 7 either detectable or undetectable), and (iii) viral loads were above the detection limit on days 7 and 14. For the primary analysis, we chose a detection limit of 15 IU/ml to be consistent with commercial HCV assays such as the Cobas TaqMan HCV quantitative assay (Roche Diagnostics). A sensitivity analysis is presented in the Supplementary Information using an HCV detection limit of 1 IU/ml.

### *Generation of in silico individuals with recent HCV infection*

Individuals recently infected with HCV have not been frequently sampled in clinical trials and therefore, parameter distributions specific to recent HCV infection have not been established. Therefore, we generated *in silico* people with recent HCV infection using the same procedure and parameter distributions as described for the generation of *in silico* people with chronic HCV infection in the previous section. Based on the available literature, adjustments were made to the baseline viral loads $V(0) \in (10^4, 10^8)$ IU/mL and the detection limit of 10 IU/mL in clinical trials (*11, 12*).

### *Time to cure (TTC)*

As previously employed (*15-23*), the TTC was defined as the time to reach less than one HCV particle in the entire extracellular body fluid (i.e., 15 L), corresponding to a viral load threshold of $V = 7 \times 10^{-5}$ IU/mL. TTC has a ceiling of 12 weeks for all DAA regimens except P/G for which we imposed a ceiling of 8 weeks (*24*).

## Results

### *Modeling suggests 5 weeks of treatment duration for people with chronic HCV infection when viral load is undetectable on-treatment on day 7*

Among *in silico* individuals with chronic HCV infection, 27% had a detectable viral load on day 7 and day 14, assuming a detection limit of 15 IU/mL (**Fig.1A**). Approximately a quarter of *in silico* people with chronic HCV infection were undetectable on day 7 and ~73% *in silico* people with chronic HCV infection had undetectable viral loads on day 14 (**Fig.1B/C**).

Analysis of TTC of the entire cohort of 100,000 *in silico* people with chronic HCV infection predicted that ~89%, ~76% and ~50% can be cured within 8, 6 and 4 weeks of treatment, respectively. Further analysis predicted that chronically infected *in silico* individuals with undetectable viral loads on day 14 but detectable viral loads on day 7, which represents ~49% of all *in silico* individuals, can achieve 90% and 95% SVR with 6 and 7 weeks of therapy, respectively (**Fig.1B**). The median TTC in this subset of individuals was 28 days [min=18 days, max=66 days].

A similar analysis of TTC of *in silico* people with chronic HCV infection who have undetectable viral loads on days 7 and 14, which represents ~25% of all *in silico* people with chronic HCV infection, suggested that 4 and 5 weeks of therapy is sufficient to achieve 90% and 95% SVR, respectively (**Fig.1C**). The median TTC in this subset of individuals was 19 days [min=11 days, max=59 days].

For *in silico* people with chronic HCV infection with detectable viral loads on days 7 and 14, we found that the standard care of duration is recommended for 95% SVR (**Fig.1A**). The median TTC in this subset of individuals was 52 days [min=30 days, max=84 days].

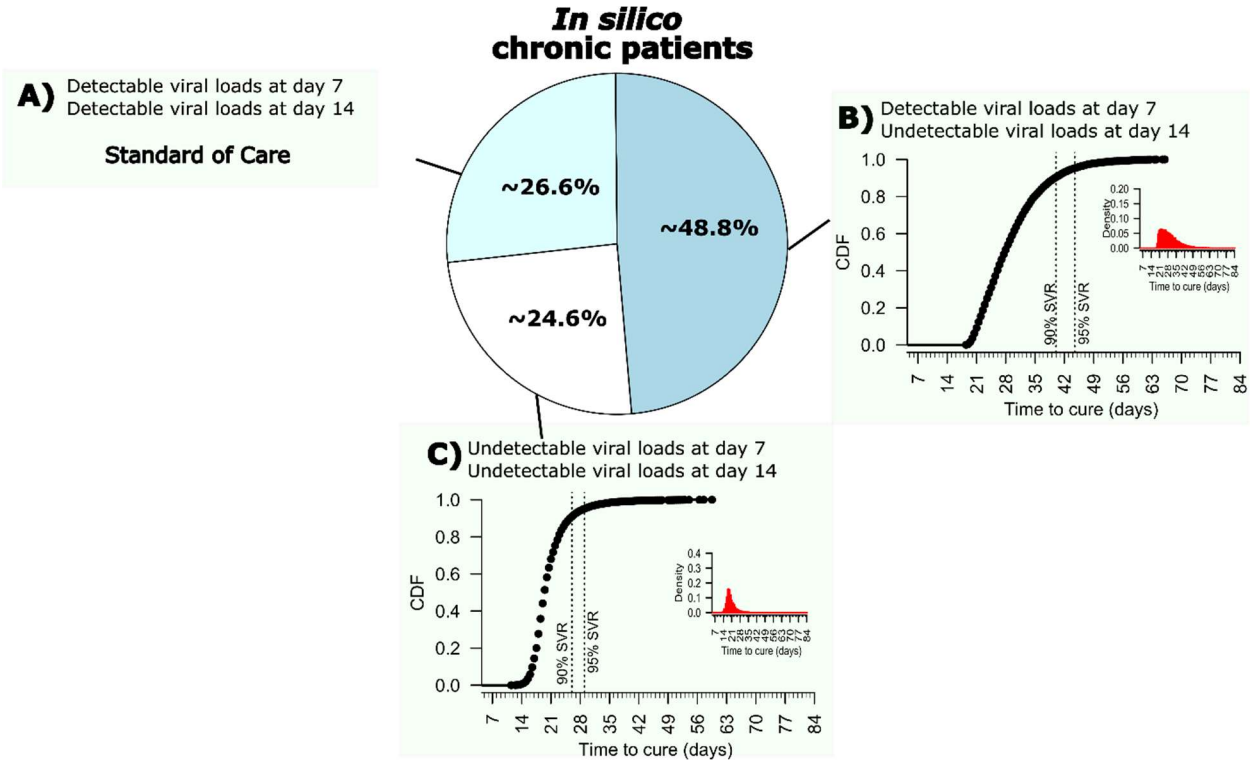


**Figure 1:** Cumulative density function (CDF) of time to cure (sustained viral response, SVR) of *in silico* people with chronic HCV infection with **(A)** detectable viral loads on days 7 and 14, **(B)** viral loads detectable on day 7 but undetectable on day 14, and **(C)** undetectable viral loads on days 7 and 14. Inlets in (A,B,C) show frequency distributions. Here, TTC represents the time when viral loads of an *in silico* individual drop below the cure boundary ($7x10^{-5}$ IU/mL). Detection limit is assumed to be 15 IU/mL.

Overall, our modeling approach predicted that duration of treatment can be shortened to 5 weeks for people with chronic HCV infection when viral load is undetectable on-treatment on day 7 (**Fig. 3**). Similarly, treatment can be shortened to 7 weeks when viral load is undetectable on day 14.

***Modeling suggests 5 weeks of treatment duration for individuals with recent HCV infection when viral load is undetectable on-treatment on day 7***

We generated *in silico* individuals with recent HCV infection treated with P/G as described in Methods. To mimic the clinical trials (*11, 12*), we assumed a detection limit of 10 IU/mL. Approximately 27% of recently infected *in silico* individuals had a detectable viral load on day 7 and day 14 (**Fig.2A**), ~32% were undetectable on day 7 (**Fig2.C**) and 73% were undetectable on day 14 (**Fig 2B/C**).

Similar to the analysis of *in silico* chronically HCV-infected individuals, analysis of TTC of the entire cohort of 100,000 *in silico* recently HCV-infected individuals treated with P/G predicted that ~52% and ~78% and can be cured within 4 and 6 weeks of P/G treatment, respectively.

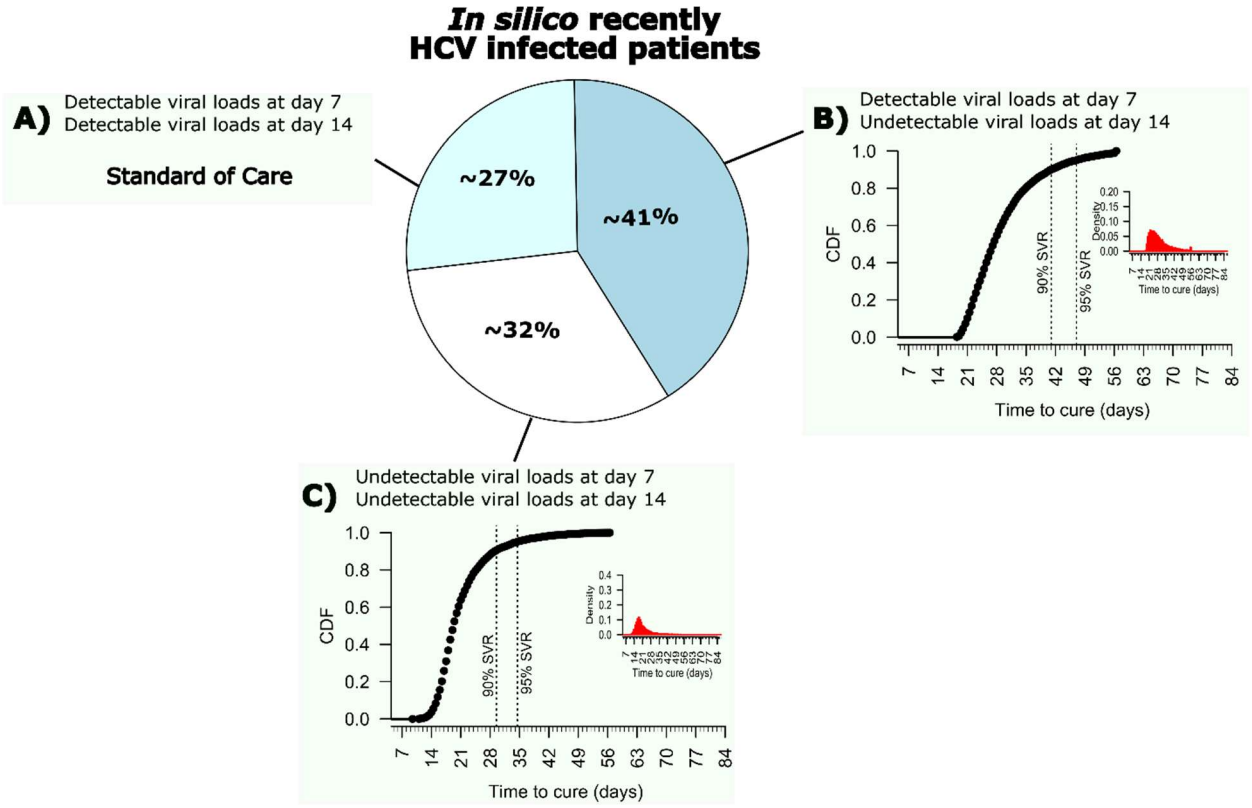


**Figure 2:** Cumulative density function (CDF) of time to cure (sustained virological response, SVR) of *in silico* people with recent HCV infection with **(A)** detectable viral loads on days 7 and 14, **(B)** viral loads detectable on day 7 but undetectable on day 14, and **(C)** undetectable viral loads on days 7 and 14. Inlets in (A,B,C) show frequency distributions. Here, Time to cure represents the time when viral loads of an *in silico* individual drops below the threshold for cure ($7x10^{-5}$ IU/mL). Detection limit is assumed to be 10 IU/mL.

We found that 5 weeks of P/G treatment is sufficient to achieve 95% SVR when viral loads are undetectable on day 7, which was identified in ~32% of people with recent HCV infection *in our in silico analysis* (**Fig.2C**). The median TTC in this subset of individuals was 19 days [min=9 days, max=56 days].

When viral loads are detectable on day 7 but undetectable on day 14, which was identified in ~41% of *in silico* individuals with recent HCV infection, 6 and 7 weeks of P/G treatment were predicted to achieve 90% and 95% SVR (**Fig.2B**). The median TTC in this subset of individuals was 27 days [min=18 days, max=56 days]. When viral loads are detectable on day 7 and day 14, 8 weeks of P/G treatment is supported by our analysis (**Fig.2A**).

Overall, we project that ~32% of people with recent HCV infection with undetectable viral loads on day 7 can potentially reduce their treatment duration to 5 weeks (**Fig.3**).

We propose a simplified treatment flowchart for individuals with chronic or recent infection (**Fig.3**).

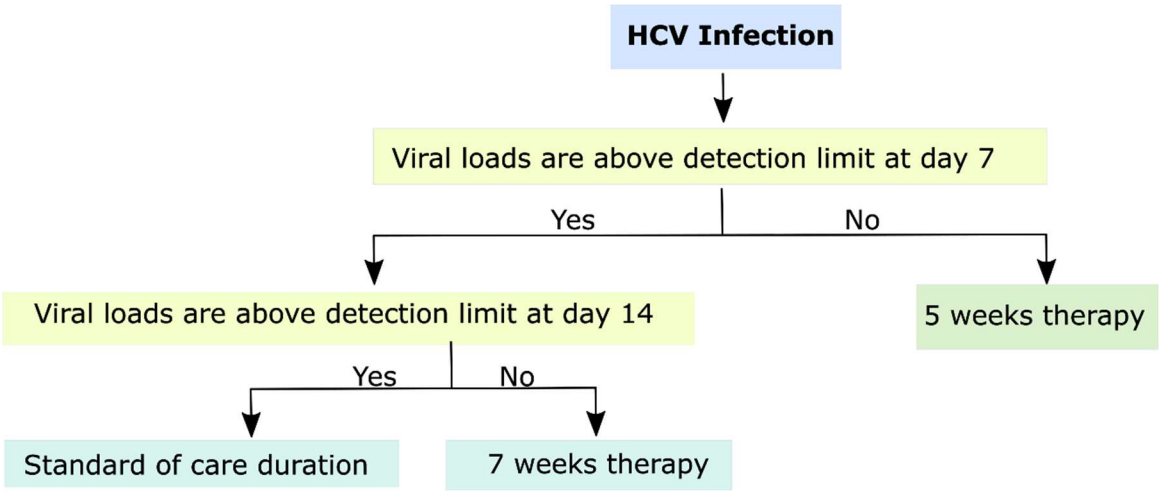


**Figure 3: Proposed treatment flowchart for people with chronic or recent HCV infection when viral loads are measured on days 7 and 14**: The flowchart is based on 10,000 *in silico* people with chronic HCV infection with baseline viral loads ∈ [$10^5$, $10^{7.5}$] IU/mL and 10,000 *in silico* people with recent HCV infection with baseline viral loads ∈ [$10^4$, $10^8$] IU/mL. If viral loads are detectable on day 14, then standard of care duration is recommended. If viral loads are undetectable on day 14, then 7 weeks of therapy is recommended for people with chronic and recent HCV infection, respectively. If viral loads are undetectable on day 7, then 5 weeks of therapy is recommended for people with chronic and recent HCV infection, respectively. Standard of care duration is 12 weeks for all DAAs that were used to treat chronic infection in the training set except P/G treatment for which 8 weeks is recommended. P/G, glecaprevir-pibrentasvir.

## Discussion

In our previous study based on available longitudinal viral load data from a clinical trial in 10 people with chronic HCV infection (*9*), we predicted that day 7 and day 14 are critical to ensure accurate predictions of the TTC using a RGT approach. To build on these important results, we generated large *in silico* populations of individuals with chronic and recent HCV infection and predicted SVR based on whether HCV was detectable on day 7 and day 14 of DAA treatment. The *in silico* populations were generated leveraging data from available small well-characterized datasets with intensive early HCV monitoring to increase statistical power and to facilitate sensitivity analysis (see Supplemental Information) regarding the detection limit of HCV RNA. We assessed whether treatment duration can be reduced for people with recent and chronic HCV infection while maintaining an SVR of >95%. We were particularly interested in shortening treatment duration for individuals with undetectable viral loads at day 7 and/or day 14 of treatment because measurements are available at these timepoints in some clinical trials and HCV RNA levels at day 14 were found to identify individuals at risk for relapse (*25*).

We had a high degree of confidence that our *in silico* populations were representative because the viral kinetics and the predicted SVR rates of the *in silico* populations (**SFig.1A** and **SFig.1B**) closely matched real world data. For example, ~50-70% of *in silico* people with chronic HCV infection had undetectable viral loads at day 14, within the range of 30%-70% observed in clinical trials (*10, 26, 27*). Furthermore, analysis of TTC of *in silico* people with chronic HCV infection predicted that ~50% and ~76% individuals could be cured with 4 weeks and 6 weeks of

treatment, respectively. This is also similar to observed SVR12 rates of ~50% (*28*) and ~67% (*29*), respectively, in clinical trials. With regard to recent infection, ~73% of *in silico* individuals had undetectable viral loads at day 14, similar to ~68% from two recently concluded clinical trials with P/G treatment (*13, 14)*. Our analysis of *in silico* people with recent HCV infection with undetectable viral load at day 14 predicted SVR rates of ~71% and ~95% with 4 and 6 weeks of treatment respectively. Similarly, in clinical trials of people with recent HCV infection who had undetectable viral loads at day 14, ~87% and 100% achieved SVR with 4 and 6 weeks of treatment, respectively (*11, 12*). In general, 4 weeks of P/G treatment has resulted in SVR12 rates of >75% in people with recent HCV infection (*12, 30*) and ~60-90% in people with chronic HCV infection (*31*).

We chose an HCV detection limit of ~15 IU/mL for our primary analysis of chronically infected individuals to be consistent with the clinically available COBAS AmpliPrep and Cobas TaqMan HCV quantitative assay (Roche Diagnostics). Our analysis predicted that 5 and 7 weeks of therapy is required to achieve >95% SVR when on-treatment day 7 and day 14 viral loads, respectively, are undetectable. A recent clinical trial in which 39 chronically infected individuals who had undetectable HCV at day 7 and received 4 weeks of treatment reported only about an 80% SVR rate (*26, 32*). Our analysis suggests that such individuals could have benefitted from an additional week of therapy.

Our analysis of recently infected individuals also predicted that 5 and 7 weeks of P/G treatment is required to achieve >95% SVR when on-treatment day 7 and day 14 viral loads, respectively, are undetectable. An HCV detection limit of ~10 IU/mL was used to be consistent with the clinical trials data used to generate the *in silico* population with recent infection. We believe that our predicted treatment duration for people with recent HCV infection is likely an overestimation since viral loads on day 14 and day 28 were consistently higher by ~0.5log10 in *in silico* individuals with recent infection compared to real world individuals with HCV infection (**SFig.1B**). Despite this consideration, it is estimated that ~32% of people with recent HCV infection with undetectable viral loads on day 7 can potentially cut their treatment duration by at least 2 weeks, thus conserving valuable resources.

Overall, modeling predicts shortening of DAA treatment duration to 5 weeks in individuals with recent or chronic infection with HCV RNA undetectable at day 7 on treatment, if the detection limit of the assay is 10-15 IU/mL. The full treatment flowchart for recently and people with chronic HCV infection is provided in **Figure 3**. We performed a sensitivity analysis to assess the impact of using a theoretical ultra-sensitive HCV assay (see Supplementary Information). Modeling predicted that DAA treatment duration could be reduced to 4 weeks in individuals with recent or chronic infection with HCV RNA undetectable at day 7, if theoretically the detection limit of the assay is 1 IU/mL. Thus, the sensitivity of the HCV assay used at early on treatment timepoints plays an important role in optimizing duration of therapy.

Despite its usefulness, there are some limitations of the current approach. First, we assumed that treatment specific parameter distributions were similar for P/G and other DAAs despite that the standard duration of P/G treatment is 8 weeks, while it is 12 weeks for other treatment regimens. This assumption is supported by (i) the comparable early viral kinetics for P/G and the other DAA regimens, that determine TTC (**SFig.2**), and (ii) the recent Resolve study reporting that SOF/VEL could be given for 8 weeks to people with chronic HCV infection who are both treatment naïve and non-cirrhotic (*33*). Secondly, we assumed that infection specific parameter distributions for recently infected HCV individuals were similar to those of people with chronic HCV infection due to limited data in those with recent infection. Overall, this assumption led to conservative estimates of optimal duration of therapy for recently infected individuals. When more data becomes available in the future, it will be important to interrogate the assumption of similar viral dynamics between individuals with recent HCV infection and chronic HCV infection. If differences were to be found, the development of a model capturing the viral dynamics in individuals with recent HCV infection is suggested. It will also be important to investigate if viral dynamics differ between DAAs which could allow for a further reduction in treatment duration for a subset of DAAs without compromising SVR rates.

In summary, we have developed a simplified algorithm to reduce duration of DAA treatment for HCV that does not require modeling or knowledge of infection stage i.e., recent or chronic. The flowchart presented in **Figure 3** can be implemented in clinical settings to validate and refine the predictions based on the *in silico* analysis. The proposed approach could reduce cost and increase patient engagement and adherence, particularly in populations such as people who inject drugs (7), co-infected with human immunodeficiency virus (*34*) and pregnant women (*35*). Overall, it is estimated that ~73% of chronically infected individuals who receive a standard 12-week DAA treatment regimen will have undetectable viral loads at day 7 and/or day 14 and could reduce their treatment duration to 5 weeks, thus, saving valuable resources. The first point of care (POC) qualitative assay was recently approved by the FDA (*36*) and others are in development (*37*). Currently the detection limit is relatively high in POC assay and varies by genotype, making it impractical to use in the proposed algorithm. In the future, more sensitive next generation POC assays could be used to further streamline the treatment process by incorporating a test and treat approach based on a qualitative result, followed by POC assessments at day 7 and day 14 to determine duration of therapy.

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**Conflicts of interest**

TK has consulted for Gilead, Abbvie, GSK. TK has had research support from Gilead and Abbvie.

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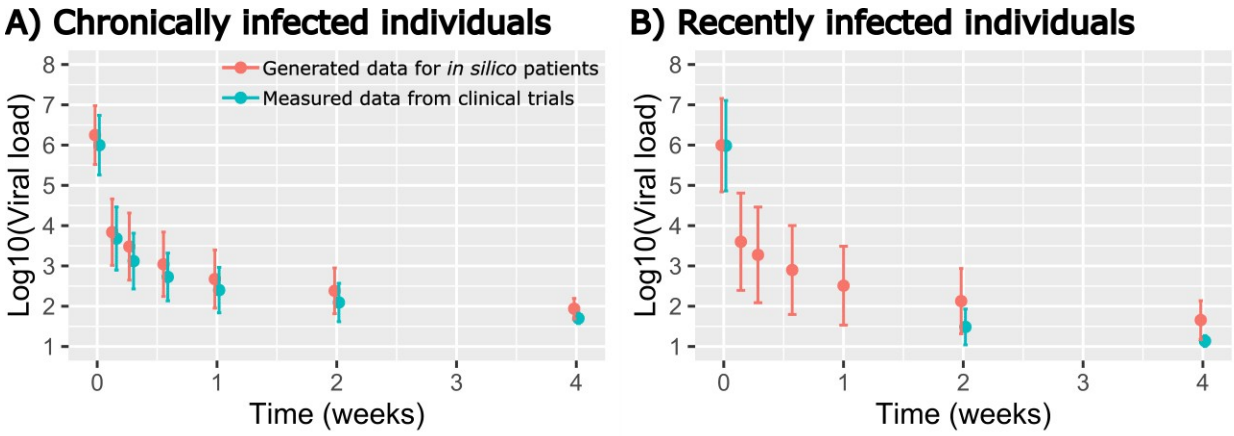
# Supplementary Material

**Sensitivity of the optimal duration of therapy to the detection limit of the HCV assay in individuals with chronic HCV infection**

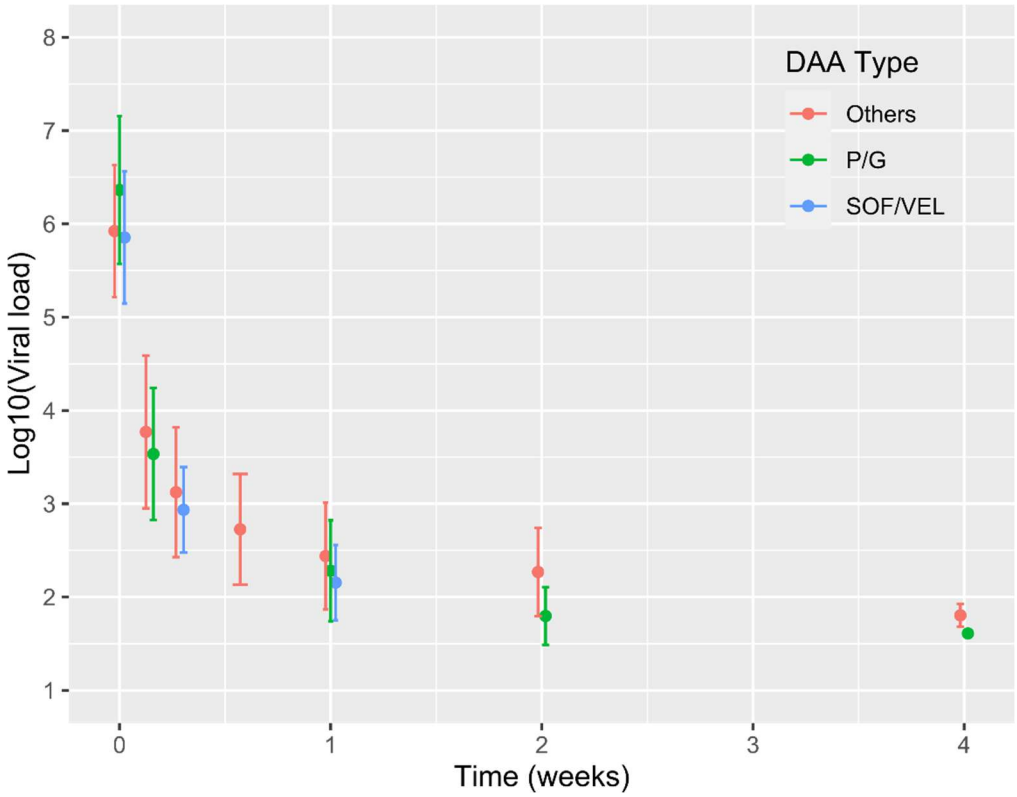
We reanalyzed the *in silico* people with chronic HCV infection in the main text using a highly sensitive detection limit of 1 IU/mL. Only ~49% of chronically infected *in silico* individuals had a detectable viral load on both days 7 and 14, ~4% had undetectable viral load on day 7 and ~51% had undetectable viral load on day 14. Our analysis of *in silico* people with chronic HCV infection with detectable viral loads on day 7 but undetectable viral loads on day 14 predicted 90% and >95% SVR with 4 and 5 weeks of therapy, respectively. A similar analysis of TTC of *in silico* people with chronic HCV infection who have undetectable viral loads on days 7 and 14 suggested that 3 and 4 weeks of therapy is sufficient to achieve 90% and >95% SVR, respectively. The analysis showed that compared to an HCV assay with a detection limit of 15 IU/ml, a more sensitive assay identified a smaller subset of individuals with undetectable HCV at early on treatment time points who required a shorter duration of therapy to achieve SVR.

**Sensitivity of the optimal duration of therapy to the detection limit of the assay in individuals with recent HCV infection**

We reanalyzed the *in silico* recent HCV infected individuals in the main text using a more sensitive detection limit of 1 IU/mL. In this case, only ~44% of recently infected *in silico* individuals had a detectable viral load on both days 7 and 14. A minority of *in silico* people with recent HCV infection (~13%) were undetectable on day 7 while ~56% *in silico* people with recent HCV infection had undetectable viral loads on day 14. Our analysis of *in silico* people with recent HCV infection with detectable viral loads on day 7 but undetectable viral loads on day 14 predicted 90% or >95% with 5 and 6 weeks of therapy, respectively. A similar analysis of TTC of *in silico* people with recent HCV infection who have undetectable viral loads on days 7 and 14 suggested that 3 and 4 weeks of therapy is sufficient to achieve 90% and >95% SVR, respectively. The analysis showed that compared to an HCV assay with a detection limit of 10 IU/ml, a more sensitive assay identified a smaller subset of individuals with undetectable HCV at early on treatment time points who required a shorter duration of therapy to achieve SVR.




**SFigure 1: (A)** Comparison of mean (round marker)±sd (vertical lines) between *in silico* generated people with chronic HCV infection (*red*) and data from 266 individuals from clinical trials (teal) (*10*). We generated *in silico* people with chronic HCV infection with the baseline viral loads $V(0)$ ($10^5$, $10^{6.8}$) IU/mL by simulating multiscale model with a random parameter set of viral dynamics- and treatment-specific parameters as described in Methods in the main text. **(B)** Comparison of mean (round marker)±sd(vertical lines) between *in silico* generated people with chronic HCV infection (*red*) and data from 53 people with recent HCV infection treated with Glecaprevir-pibrentasvir in two clinical trials (teal) (*11, 12*). We generated *in silico* people with recent HCV infection with the baseline viral loads $V(0)$ ($10^4$, $10^8$) IU/mL by simulating multiscale model with a random parameter set of viral dynamics- and treatment-specific parameters as described in Methods in the main text.




**SFigure 2: Viral kinetics stratified by the type of DAA.** Mean (round marker)±sd (vertical lines) of the data from 266 individuals from clinical trials from multiple studies as listed in (*10*). We focused on two DAAs, namely P/G and SOF/VEL, while combining all other DAAs as others. The data show that the early viral kinetics were similar for the three groups.