Modeling-Based Response-Guided DAA Therapy for Chronic Hepatitis C to Identify Individuals for Shortening Treatment Duration

Ashish Goyal,1 Alex Churkin,2 Danny Barash,2 Scott J. Cotler,3 Amir Shlomai,4 Ohad Etzion,5,6 and Harel Dahari1

1The Program for Experimental and Theoretical Modeling, Division of Hepatology, Stritch School of Medicine, Loyola University Chicago, Maywood, Illinois, USA, 2Department of Software Engineering, Sami Shamoon College of Engineering, Beer-Sheva, Israel, 3Department of Computer Science, Ben-Gurion University, Beer-Sheva, Israel, 4Department of Medicine D and The Liver Institute, Rabin Medical Center, Belinson Hospital, Petah-Tikva and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, 5Soroka University Medical Center, Beer-Sheva, Israel, and 6The Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Shortening duration of direct-acting antiviral therapy for chronic hepatitis C could provide cost savings, reduce medication exposure, and foster adherence and treatment completion in special populations. The current analysis indicates that measuring hepatitis C virus at baseline and on days 7 and 14 of therapy can identify patients for shortening therapy duration.

Keywords. direct-acting antivirals; hepatitis C virus; mathematical modeling; response-guided therapy; time to cure.

The advent of all-oral direct-acting antivirals (DAAs) has transformed the landscape of hepatitis C virus (HCV) therapy and paved the path to the ambitious World Health Organization goal of viral hepatitis elimination by 2030 [1]. However, several remaining challenges such as DAA cost and treatment of HCV in special populations must be overcome to achieve this goal [2, 3]. Shortening duration of DAA therapy could provide cost savings [4–7], reduce medication exposure (eg, during pregnancy [8]), and help to foster adherence and treatment completion in general [9] and specifically in special populations (eg, people who inject drugs [2] and incarcerated individuals [10]), which is key to achieving cure [11]. Thus, identifying individuals for shortening DAA therapy duration is warranted.

We recently reported a proof-of-concept study [12] demonstrating that real-time (ie, on treatment) mathematical modeling–based (Figure 1A) response-guided therapy (RGT) with DAA for chronic HCV infection can be utilized for shortening DAA duration without compromising treatment efficacy. The proof-of-concept study [12] relied on measuring HCV at baseline and on days 2, 7, 14, and 28 after initiation of DAA therapy, which is cumbersome in clinical practice. We also reported [12] that all patients (but 1) in whom viral load was reduced to <14 IU/mL at day 14 after initiation of treatment were predicted to reach cure on a shortened duration of DAA therapy, suggesting that measuring viral load at day 28 may not be needed.

As reducing the number of HCV measurements would facilitate large-scale implementation of the RGT approach, we aim in the current study to retrospectively investigate whether some HCV measurement time points in the proof-of-concept study (ie, days 2, 7, 14, and/or 28) can be excluded without compromising the ability to predict the DAA therapy duration needed to reach cure.

METHODS

Mathematical Model

The typical HCV RNA decline pattern on DAA therapy is biphasic and consists of a first rapid viral decline phase, lasting ~1–2 days, followed by a slower second phase decline [5, 13]. Thus, the standard biphasic model (Figure 1A) [14] was used:

\[
\begin{align*}
\frac{dI}{dt} &= \beta VT_0 - \delta I \\
\frac{dV}{dt} &= (1 - \varepsilon)pI - cV,
\end{align*}
\]

where \(T_0\) represents the number of susceptible target cells, \(I\) the number of infected cells, and \(V\) the HCV level in blood. HCV (\(V\)) infects \(T_0\) with the rate constant \(\beta\), generating infected cells (\(I\)), which produce \(V\) at rate \(p\) per infected cell. Infected cells are lost at a rate of \(\delta\) per infected cell, and virions are assumed to be cleared from blood at a rate of \(\varepsilon\) per virion. DAA efficacy, \(\varepsilon\), in blocking viral production from infected cells is assumed to be between 0 and 1 (where 1 = 100% efficacy).

Initial Parameter Estimations

Similar to our proof-of-concept study [12], we assumed that the \(T_0\) level remained constant during DAA therapy. The pretreatment (time, \(t = 0\)) infected cell level \(I(0)\) is represented by the steady state pretreatment level of \(I(0) = \frac{\beta T_0 V(0)}{\delta}\), where \(V(0)\) is the
the pretreatment measured viral load of each patient. The viral production rate constant was set to pretreatment level $p = \frac{5V(0)}{1000}$. We previously showed \cite{14, 15} that Equation 1 can be solved analytically independently of $\beta$, $p$, and $T_0$. Therefore, we arbitrarily fixed $\beta = 3.5 \times 10^{-8}$ mL/virion/d and $T_0 = 1 \times 10^7$ cells/mL.

**Time to Cure**

As previously done \cite{4-6, 12, 16-20}, time to cure (TTC) was defined as the time to reach <1 HCV particle in the entire extracellular body fluid. For example, a value of 1 virus copy in 15 L of extracellular body fluid volume, that is, $V = 7 \times 10^7$ IU/mL, was used as the threshold for cure.

**Model Fitting Procedure**

The biphasic model (Equation 1) was fitted using the Levenberg-Marquardt algorithm embedded in the function “lsqnonlin” in Matlab R2021a (The Mathworks, Natick, MA, USA), with the measured HCV kinetic data obtained from the 10 patients in the proof-of-concept study \cite{12} for whom the model was applied during treatment to shorten standard DAA therapy. Live Matlab scripts are provided in Churkin et al. \cite{21}.

Starting with different initial guesses for each unknown parameter ($c$, $\delta$, and $\epsilon$), the fitting procedure consisted of finding 1000 model parameter sets of best fits ($c \in [1, 25]$/day, $\delta \in [0.1, 1.5]$/day, and $\epsilon \in [0.90, 0.9999]$) and recording corresponding goodness of fit using corrected Akaike Information Criteria (AIC) \cite{22}. The duration of the first viral decline phase and TTC were estimated (Figure 1B). In the final step, we only accepted TTC from those best fits that were within 2 points of the lowest AIC, and those with a duration of the first phase ≤2.5 days. The first data point below detection or below the lower limit of quantification was assigned a value ($\epsilon \in [0.2, 15]$ IU/mL). We explored removing day 28 and either day 2 or day 7 from the 10 patients and repeated the same procedure, projecting TTC using truncated data.

**Linear Regression Procedure**

We also explored using linear regression (ie, lm function in R) to predict TTC using only HCV measurements on days 7 and 14.

**Patient Consent**

The study was approved by the institutional review boards of Soroka and Rabin Medical Centers and was conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. All patients provided written informed consent.

**RESULTS**

We first confirmed that TTC for each of the 10 patients, using all the measured data points, was in agreement with the estimated TTC reported in Table 1 \cite{12}. In 2/10 patients (P8 and P9), HCV at day 28 was detected and was used for predicting TTC as in Etzion et al. \cite{12}. Excluding day 28 in these 2 patients had a limited effect on maximum TTC projections, leading to underprediction by 2 days in P8 and overprediction by 6 days in P9 (Table 1).

Further excluding the day 2 HCV measurement had a limited effect on maximum TTC projections (Figure 1B vs Supplementary Figure 1A), which remained accurate in 8/10 cases (Figure 1C, Table 1). In 2 patients (P3 and P7), this strategy led to underprediction by 4 and 8 days, respectively (Table 1). In contrast, excluding day 7 disproportionality affected the maximum TTC projections, resulting in over- or underprediction by at least 1 week in 6 individuals (Figure 1C) and overprediction by about 5 weeks in 2 additional patients (P2 and P4) (Table 1). Interestingly, applying linear regression using only day 7 and day 14 measurements for estimating TTC...
agreed with the TTC estimated by fitting the model (Equation 1) excluding day 2 (Table 1) in all but 1 case (P3, for whom linear regression could not be employed due to a missing day 7 measurement).

### DISCUSSION

In the current study, we retrospectively modeled proof-of-concept trial data to further examine whether some monitoring time points may be removed without affecting TTC prediction. Modeling results indicated that on-treatment day 2 and day 28 clinical visits may not be necessary as their exclusion had a limited impact on TTC predictions. In a minority of cases, however, this strategy led to underprediction by at most 8 days, the impact of which can be offset by a precautionary 1-week extension of the predicted TTC. In contrast, missing day 7 measurement disproportionality affected the maximum TTC projections, resulting in over- or underprediction by at least 1 week in 6 individuals. A possible explanation for the importance of the day 7 measurement over day 2 is that days 7 and 14 constitute the final phase of viral decline (ie, the second phase in the biphasic model), whereas day 2 could be part of a transient phase that precedes the final phase, as we previously reported [23]. Thus, day 7 and day 14 measurements play a key role in predicting TTC.

Applying linear regression on only day 7 and day 14 measurements also predicted TTC accurately in all patients but 1 (P3), in whom day 7 measurement was missing. As the modeling approach (Equation 1) included the pretreatment measured viral load, it was still possible to predict TTC in P3 without day 7 (Table 1). In addition, linear regression could lead to overestimation of TTC compared with the modeling-based approach, as shown for a hypothetical patient in Supplementary Figure 2.

These examples highlight the limitations of using linear regression to predict TTC based on viral measurements at days 7 and 14 and support the use of modeling to make TTC predictions.

Three parameters (c, δ, and ϵ) were estimated for each patient to predict TTC. The general rule of thumb in the parameter estimation procedure dictates that more data points than the number of estimated parameters are needed [24]. As we aim to minimize the number of on-treatment HCV measurements to 3 (ie, baseline, days 7 and 14), the 3 viral kinetic parameters (c, δ, and ϵ) cannot be estimated with confidence (nonidentifiability issues), as shown for a representative case (P6 in Supplementary Figure 1B). However, despite these nonidentifiability issues, the overarching goal of accurately predicting TTC remains largely unaffected (Figure 1B; Supplementary Figure 1A).

### CONCLUSIONS

The current analysis indicates that on-treatment day 2 and day 28 HCV measurements are not critical for predicting TTC. Measuring HCV at baseline and on days 7 and 14 after initiation of DAA therapy provides a simplified and more practical on-treatment monitoring procedure during modeling-based RGT that can be readily adopted in clinical practice. Further validation in a large-scale clinical trial will support the routine implementation of our individualized treatment approach in patients receiving DAA for chronic hepatitis C.

### Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.
References

1. Thomas D. Global elimination of chronic hepatitis. N Engl J Med 2019; 380:2041–50.
2. Hayes CN, Imanura M, Tanaka J, et al. Road to elimination of HCV: clinical challenges in HCV management. Liver Int. In press. doi:10.1111/liv.15150.
3. Graham CS. The current status of US and global access to direct-acting antiviral regimens for hepatitis C virus infection. Clin Liver Dis (Hoboken) 2020; 16:16–9.
4. Dasgupta S, Imanura M, Gorstein E, et al. Modeling-based response-guided therapy for chronic hepatitis C under glecaprevir/pibrentasvir may identify patients for ultra-short treatment duration. J Infect Dis 2020; 222:1165–9.
5. Dahari H, Canini L, Graw F, et al. HCV kinetic and modeling analyses indicate similar time to cure among sofosbuvir combination regimens with daclatasvir, simeprevir or ledipasvir. J Hepatol 2016; 64:1232–9.
6. Gambato M, Canini L, Lens S, et al. Early HCV viral kinetics under DAs may optimize duration of therapy in patients with compensated cirrhosis. Liver Int 2019; 39:826–34.
7. Zhuo Y, Hayashi T, Chen Q, et al. Estimating the price at which hepatitis C treatment with direct-acting antivirals would be cost-saving in Japan. Sci Rep 2020; 10:4089.
8. Kushner T, Terrault NA. Hepatitis C in pregnancy: a unique opportunity to improve the hepatitis C cascade of care. Hepatol Commun 2019; 3:20–8.
9. Welzel TM, Yang M, Sajeev G, et al. Assessing patient preferences for treatment decisions for new direct acting antiviral (DAA) therapies for chronic hepatitis C virus infections. Adv Ther 2019; 36:2475–86.
10. Akiyama MJ, Kronfi N, Cabezas J, et al. Hepatitis C elimination among incarcerated prisons: challenges and recommendations for action within a health systems framework. Lancet Gastroenterol Hepatol 2021; 6:391–400.
11. Su J, Lim JK. Is real-life hepatitis C virus therapy as effective as in clinical trials? In Clinical Dilemmas in Viral Liver Disease. 2nd ed. Foster GR, Reddy RK, eds. Wiley; 2020:138–142.
12. Etzioni O, Dahari H, Yardeni D, et al. Response guided therapy for reducing duration of direct acting antivirals in chronic hepatitis C infected patients: a pilot study. Sci Rep 2020; 10:17820.
13. Dahari H, Guedj J, Perelson AS, et al. Hepatitis C viral kinetics in the era of direct acting antiviral agents and IL28B. Curr Hepat Rep 2011; 10:214–27.
14. Neumann AU, Lam NP, Dahari H, et al. Hepatitis C virus dynamics in vivo and the antiviral efficacy of interferon alpha therapy. Science 1998; 282:103–7.
15. Dahari H, Lo A, Ribeiro RM, et al. Modeling hepatitis C virus dynamics: liver regeneration and critical drug efficacy. J Theor Biol 2007; 247:371–81.
16. Goyal A, Lurie Y, Meissner EG, et al. Modeling HCV cure after an ultra-short duration of therapy with direct acting agents. Antiviral Res 2017; 144:281–5.
17. Dahari H, Sheingart S, Gafanovich I, et al. Sustained virological response with intravenous silibinin: individualized IFN-free therapy via real-time modelling of HCV kinetics. Liver Int 2015; 35:289–94.
18. Dixit NM, Layden-Almer JE, Layden TJ, et al. Modelling how ribavirin improves interferon response rates in hepatitis C virus infection. Nature 2004; 432:922–4.
19. Gorstein E, Martinello M, Churkin A, et al. Modeling based response guided therapy in subjects with recent hepatitis C infection. Antiviral Res 2020; 180:104862.
20. Canini L, Imanura M, Kawakami Y, et al. HCV kinetic and modeling analyses project shorter durations to cure under combined therapy with daclatasvir and asunaprevir in chronic HCV-infected patients. PLoS One 2017; 12:e0187409.
21. Churkin A, Kriss S, Uziel A, et al. Machine learning for mathematical models of HCV kinetics during antiviral therapy. Math Biosci 2022; 343:108756.
22. Akaike, H., Information theory and an extension of the maximum likelihood principle. In Selected Papers of Hirotugu Akaike. Parzen E, Tanabe K, Kitagawa G, eds. Springer; 1998:199–213.
23. Guedj J, Dahari H, Rong L, et al. Modeling shows that the NSSA inhibitor daclatasvir has two modes of action and yields a shorter estimate of the hepatitis C virus half-life. Proc Natl Acad Sci U S A 2013; 110:3991–6.
24. Jacquez JA. Identifiability and parameter estimation. J PEN J Parenter Enteral Nutr 1991; 15:533–95.