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Modeling based response guided therapy in subjects with recent hepatitis C infection

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ABSTRACT

Background & aims: Mathematical modeling of viral kinetics has been shown to identify patients with chronic hepatitis C virus (HCV) infection who could be cured with a shorter duration of direct-acting antiviral (DAA) treatment. However, modeling therapy duration has yet to be evaluated in recently infected individuals. The aim of this study was to retrospectively examine whether modeling can predict outcomes of six-week sofosbuvir (SOF) and weight-based ribavirin (R) therapy in individuals with recent HCV infection.
Methods: Modeling was used to estimate viral host parameters and to predict time to cure for 12 adults with recent HCV infection (<12 months of infection) who received six weeks of treatment with SOF + R.
Results: Modeling results yielded a 100% negative predictive value for SOF + R treatment response in nine participants and suggested that a median of 13 [interquartile range: 8–16] weeks of therapy would be required for these patients to achieve cure. Modeling predicted cure after 5 weeks of therapy in the only modeled participant who achieved a sustained virological response. However, cure was also predicted for two participants who relapsed following treatment.
Conclusions: The modeling results confirm that longer than 6 weeks of SOF + R is needed to reach cure in individuals with recent HCV infection. Prospective real-time modeling under current potent DAA regimens is needed to validate the potential of response-guided therapy in the management of recent HCV infection.

1. Introduction

Progress toward eliminating hepatitis C virus (HCV) infection was accelerated by the introduction of all-oral direct-acting antivirals (DAAs) in 2014. The development of potent DAA regimens has resulted in cure rates exceeding 90% after 8–12 weeks of treatment. While DAAs have transformed the management of chronic HCV, there is still much to learn about optimizing DAA treatment for patients with recently acquired infections. Observational and modeling studies have suggested the potential for a treatment-as-prevention effect with expanded access and high uptake of DAA therapy (Boerekamps et al., 2018; Echevarria et al., 2019; Iversen et al., 2019; Martin et al., 2016; Martinello et al., 2019b; Salazar-Vizcaya et al., 2016). A recent modeling study showed that diagnosis and treatment of people with acute HCV infection (duration of infection <6 months) led to better health and economic outcomes (Bethea et al., 2018). While it has been well-documented that interferon-α therapy (IFN) was much more effective if treatment was administered early after infection (Martinello and Matthews, 2015), pilot studies of DAA therapy for acute (<6 months) and recent (<12 months) HCV infection have demonstrated variable efficacy (sustained

Abbreviations: HCV, hepatitis C virus; SOF, sofosbuvir; R, ribavirin; GLE-PIB, glecaprevir-pibrentasvir; DAA, direct-acting antiviral; SVR, sustained virological response; DARE C II, DAA-Based Therapy for Recent HCV II; HIV, human immunodeficiency virus; IQR, interquartile range.

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virologic response, SVR, 32%–100%), with higher efficacy seen with more potent dual- and triple-class DAA regimens (Martinello et al., 2018).

We have shown that retrospective modeling of early HCV treatment response in people with chronic infection receiving DAA therapy can be used to predict the time until the virus is eliminated from the extracellular fluid (i.e. time to cure) (Canini et al., 2017; Dahari et al., 2016; Gambato et al., 2019). These analyses suggest the possibility of reducing treatment duration in a sizeable proportion, thereby cutting costs. More recently, we successfully implemented a prospective, real-time modeling-based approach to identify the optimal length of treatment in patients with chronic HCV infection (Etzion et al., 2018). However, modeling has yet to be evaluated for subjects with recent HCV infections. These individuals are often asymptomatic and infrequently identified (Shteyer et al., 2019).

Our prior DARE C II study of six weeks of sofosbuvir (SOF) and weight-based ribavirin (R) in adults with recent (estimated duration < 12 months) HCV infection demonstrated that this combination was safe and well tolerated, but that efficacy was suboptimal (Martinello et al., 2016). Of the 18 subjects who completed the scheduled course of therapy, only six (33%) achieved a sustained virologic response at post-treatment week 12 (SVR). Two patients (11%) had virus levels above the limit of quantification at the end of treatment (one of whom achieved spontaneous clearance more than 12 weeks post treatment), nine (50%) participants experienced relapse, and a single patient (6%) was re-infected.

The aim of this study was to examine whether mathematical modeling of the viral kinetics of the participants from the DARE C II study could retrospectively predict treatment outcomes under short-duration SOF + R therapy.

2. Methods

2.1. Participants

Nineteen participants (≥18 years) with recent HCV infection were enrolled in the DAA-Based Therapy for Recent HCV II (DARE-C II) study between October 2014 and May 2015 in hospitals in Australia (n = 4) and New Zealand (n = 1). Eligibility criteria were reported previously (Martinello et al., 2016). Study participants were predominantly male (n = 17, 89%), Caucasian (n = 14, 74%), and men who have sex with men (n = 16, 84%). The distribution of genotypes included genotype 1 (n = 13, 68%) and genotype 3 (n = 5, 26%). Fourteen participants (74%) were co-infected with human immunodeficiency virus (HIV), all of whom had HIV prior to their diagnosis of HCV, and 12 were on anti-retroviral therapy. Participants acquired HCV through injection drug use (n = 10, 53%) or sexual exposure (n = 9, 47%). The median HCV RNA level at baseline was 5.4 (4.5–6.7) $\log_{10}$ IU/ml. Eighteen participants (95%) completed the full 6 weeks of SOF + R therapy and one participant discontinued treatment after two weeks. As explained in Results, only 12 patients had sufficient viral kinetic data for modeling (Table 1).

2.2. HCV RNA measurements

HCV RNA levels were measured at baseline, hour 4, day 2, and weeks 1, 2, 4, and 6 after initiation of SOF + R along with post-treatment weeks 4, 12, and 24 (Martinello et al., 2016). Central HCV RNA testing was performed using COBAS TaqMan assay v2.0 (lower limit of quantification [LLoQ] 25 IU/mL; lower limit of detection 15 IU/mL). SVR was defined as HCV RNA target not detected (TND) 12 weeks after cessation of SOF + R. In performing kinetic analysis and model fitting, we defined detectable but not quantifiable HCV RNA measurements to be 20 IU/mL (i.e., the average of lower limit of detection and LLoQ), and we took undetectable measurements to be 1 IU/ml.

2.3. Mathematical modeling

HCV viral kinetic response to therapy was assumed to follow the standard biphasic model (Neumann et al., 1998):

$$\frac{dI}{dt} = \beta T_0 V - \delta I$$
$$\frac{dV}{dt} = (1-\varepsilon)\rho I - cV \quad (1)$$

where V, is the viral load in blood. Virus, V, infects target cells with rate constant β, generating productively-infected cells, I, which produce new virions at rate p per infected cell. Infected cells are lost at a rate δ per infected cell and virions are assumed to be cleared from blood at rate c per virion. Effect ε is defined as the therapy effectiveness $0 \le \varepsilon \le 1$ in preventing viral production/secretion. We assume that therapy was effective after a pharmacological delay, t_0. Similar to previous modeling efforts, we assume the target cell level remained constant during therapy at pre-treatment level $T_0 = c\delta/\beta p$ (Dahari et al., 2015).

Solving Eq. (1) predicts

$$V(t) = V_0(Ae^{-\lambda_1(t-t_0)} + (1-A)e^{-\lambda_2(t-t_0)}) \quad (2)$$

where

Table 1
Baseline characteristics.

Participant Number	Gender	Age	Weight (kg)	Height (cm)	Ethnicity	HCV Genotype	Mode of Acquiring HCV	HIV(Antiretroviral Therapy)	HCV Treatment Outcome[a]
2	Female	23	59.0	166	Caucasian	3a	IDU	No	SVR
4	Male	47	76.0	180.5	Caucasian	1a	IDU	No	Relapse
8	Male	31	61.1	170	Asian	1a	IDU	Yes (nevirapine, TDF, FTC)	Relapse
9	Male	73	68.1	178	Caucasian	1a	SE, MSM	Yes (etravirine, lamivudine, raltegravir)	Relapse
10	Male	39	64.0	171	Caucasian	1a	IDU	Yes (raltegravir, TDF, FTC)	Relapse
12	Male	31	94.6	186	Caucasian	1a	SE, MSM	Yes (rilpivirine, TDF, FTC)	Relapse
13	Male	44	68.0	179	Asian	1a	IDU	Yes (efarivirenz, TDF, FTC)	Relapse
14	Male	49	77.3	185	Caucasian	1a	SE, MSM	Yes (TDF, FTC)	Relapse
15	Male	54	91.1	181	Caucasian	1a	SE, MSM	Yes (efavirenz, TDF, FTC)	Relapse
17	Male	53	94.3	171	Hispanic	3a	SE, MSM	Yes (rilpivirine, TDF, FTC)	Non-response[b]
18	Male	30	79.4	190	Caucasian	1a	IDU	Yes (TDF, FTC)	Non-response
19	Male	45	90.5	186	Caucasian	3a	IDU	No	Relapse

IDU, injecting drug use; MSM, men who have sex with men. HIV, human immunodeficiency virus; SVR, sustained virological response; SE, sexual exposure; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine.

[a] Non-response, signifies that HCV RNA was quantifiable at end of treatment (EOT); Relapse, signifies quantifiable HCV RNA, confirmed as homologous virus, at post-treatment week 12 despite unquantifiable HCV RNA at EOT.

[b] Spontaneous clearance of virus more than 12 weeks post treatment observed.

$$\lambda_{1,2} = 0.5\left(c + \delta \pm \sqrt{(c-\delta)^2 + 4(1-\varepsilon)c\delta}\right) \text{ and } A = \frac{\varepsilon c}{\lambda_1 - \lambda_2}$$

2.4. Parameter estimation

For each patient, we fit our model to the measured viral kinetic data until the first TND was reached. Viral host parameter estimates of t_0, ε and δ (Eq. (2)) were obtained using a Constrained Optimization by Linear Approximation (COBYLA) algorithm (Powell, 1994; Reinharz et al., 2019). Initial viral load, V_0, was set during fitting based on each participant's measured baseline HCV RNA, and the serum virus clearance rate c was fixed at 2 d^{-1} for all participants, as explained in Results.

2.5. Cure boundary

The time to cure was defined as the time to reach less than one HCV particle in the entire extracellular body fluid (blood, interstitial and trans cellular) as previously done (Canini et al., 2017; Dahari et al., 2016; Gambato et al., 2019). The extracellular fluid volume is approximately 15 L, corresponding to a value of 7×10^{-5} for V (IU/ml) for the cure threshold. A sensitivity analysis was performed assuming 5 L–20 L of extracellular body fluid volume, corresponding to cure threshold values of 2×10^{-4} and 5×10^{-5} IU/mL, respectively. Based on an assumed number of infected hepatocytes in the liver, a more speculative time to cure of less than one virus and infected hepatocyte in the body was previously analyzed and was found to overestimate the time to cure (Dahari et al., 2016; Gambato et al., 2019). Therefore, this speculative time to cure was not analyzed in the current study.

2.6. Statistical analysis

Associations between participants' baseline characteristics, their viral kinetics, fitted model parameters, and predicted cure times were evaluated with non-parametric tests. Fisher's exact test was used for checking associations between categorical variables, and the Wilcoxon rank-sum test was used when one of the considered variables was continuous. For all analyses, a P-value, $P \leq 0.05$ was considered statistically significant. Data analyses were performed using R 3.5.0.

3. Results

3.1. Viral kinetics

Because modeling and viral kinetic analysis requires sufficient data from both the 1st and the 2nd decline phases, only 12 of 19 DARE-C II participants were included in the modelling analysis. Of the seven participants excluded from the modeling analysis, reasons for exclusion included no data at week 1 (n = 2), achieved TND at day 2 (n = 2), or achieved TND at week 1 (n = 3). Of these seven participants, 5 achieved SVR, 1 became re-infected, and 1 was lost to follow-up. As we previously reported, viral load below LLoQ by week 1 correlated strongly with treatment outcomes ($p = 0.006$) (Martinello et al., 2016), and since early unquantifiable data presented an obstacle to modeling the data, there was a strong association between treatment failure and inclusion in our modeling analysis ($p = 0.001$).

Of the 12 patients for whom sufficient data was available for modeling, only 1 achieved SVR. Clinical, demographic, and baseline viral characteristics of these 12 participants are detailed in Table 1. Median baseline HCV RNA was 6.36 (interquartile range, IQR: 5.81–6.82) log10 IU/ml. HCV RNA 4 h after initiation of SOF + R was 6.25 (5.68–6.95) log10 IU/ml (with a single modeled patient missing data for this time point) and was not significantly different ($p = 0.054$) from pre-treatment levels. Thereafter HCV RNA levels declined in a biphasic manner consisting of a rapid first phase (median slope −4.54 log/week corresponding to a HCV half-life of 11 h) that lasted for the first week, followed by a slower second phase (slope −0.52 log/week) (Fig. 1; Table 2). There was no association between baseline characteristics and viral kinetics.

3.2. Parameter estimation

Since viral kinetic data was not frequent enough to estimate all model parameters t_0, c, ε and δ simultaneously (i.e., identifiability issue), the serum virus clearance rate c was fixed at 2/d based on the calculated median half-life of 11 h thus allowing the other parameters to be estimated. Modeling results indicate a median pharmacological delay t_0 of 2.6 (IQR 1.4–3.5) hours. After the delay, the biphasic model described the data well (Fig. 1), and viral kinetic parameters for each participant were estimated (Table 3). The median treatment efficacy in blocking viral infection was $\varepsilon = 0.9995$ d^{-1}, and the median death/loss rate of infected cells δ was 0.223 (IQR 0.139–0.424) d^{-1}. There was no association between participants' baseline characteristics and viral-host parameters.

3.3. Predicting time to cure

Using the individual model fits, we calculated the time for each participant to achieve cure (Table 3 and Fig. 1). Median time to cure for all modeled participants was 10.6 (IQR 6.9–14.0) weeks. Modeling correctly predicted non-SVR in 9 individuals with six weeks of treatment and suggested that a median of 13.0 (IQR 8.4–16.3) weeks of therapy would be required in these cases. The negative predictive value of our model was thus 100%, as each participant who received a model-predicted cure-time exceeding six weeks failed to achieve SVR (relapse, n = 7; non-response, n = 2). The model correctly predicted cure after 5.1 weeks of therapy in the only modeled participant who achieved SVR (Participant 2) but incorrectly predicted cure after 4.6 and 5.0 weeks in two individuals (Participants 10 and 15) who relapsed post-treatment. There was no association between baseline characteristics, anti-retroviral therapy, and predicted time to cure.

4. Discussion

This study serves as a proof-of-concept for modeling the viral kinetics of people who receive DAA therapy for recent HCV infection. With treatment failure in 13 (68%) cases, the results of the DARE-C II study (Martinello et al., 2016) indicated that six weeks of SOF + R therapy was sub-optimal for people with recent HCV. Our retrospective analysis of 12 of the study participants, including 9 individuals with chronic HIV infection, indicate that modeling would have provided a negative predictive value of 100%. In order to assess positive predictive value, efforts should be undertaken to model the viral kinetics of individuals with recent HCV infection who are treated with a more potent DAA regimen.

Prior to the availability of DAA therapy, higher efficacy was seen with shortened duration interferon-based regimens in recent HCV, as compared with standard duration in chronic HCV infection (Martinello and Matthews, 2015). It was speculated that innate and adaptive immune responses were more robust in recent HCV compared to chronic HCV. The efficacy of various DAA regimens in recent HCV infection, including shortened treatment duration, have been evaluated. DARE-C II, which included frequent HCV RNA testing at early time points, was the first pilot study of a pan-genotypic interferon-free DAA regimen in recent HCV, and as such, the current study provides the first detailed HCV kinetic analysis and modeling of individuals with recent HCV treated with DAA therapy.

Historically, the standard biphasic model was used to explain the biphasic decline seen in chronic HCV-infected patients who were treated with daily IFN (Neumann et al., 1998). We showed that if the major effect of IFN treatment is to block the production or release of virions by infected cells ($0 < \varepsilon < 1$), the viral decline will be biphasic, with the initial slope of the first phase governed by the clearance rate of free

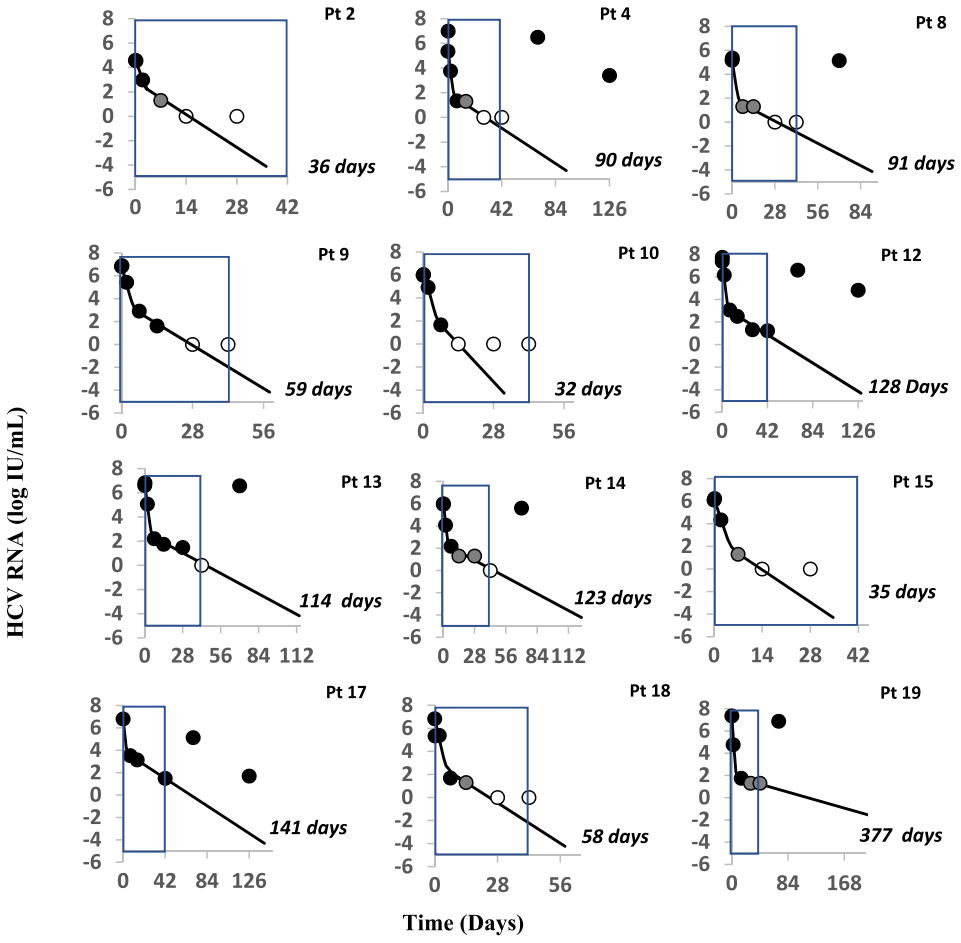

Fig. 1. Viral Kinetics Modeling Results.
Pt 2 achieved SVR. Observed viral kinetics and model predicted curves in eleven subjects, who did not achieve SVR. Black circles: quantifiable HCV; grey circles: detected, below LLoQ; open circles: below lower limit of detection; solid lines: biphasic model best fit curve, ending when cure threshold is reached; blue box represents the six weeks of therapy received by each patient. Model curves end when predicted time to cure is reached. Orange transparent box indicates the cure boundary predicted by the modeling. During modeling, the initial virus clearance, c, value was set to 2.0 d^{-1} for all 11 patients. Patient 19 only shows the curve till 300 days as model predicted time to cure that is too long to be graphed.

Table 2
Viral kinetics.

Phase	Delay	I		II	
Participant ID	$V_{BL} - V_{h4}$ (log IU/ml)	$V_{BL} - V_{w1}$ (log IU/ml)	Slope [log/week]	N	Slope [log/week]
2	0.027	3.28	−3.13	2	−1.30
4	−1.64	4.02	−5.29	3	−0.48
8	−0.19	3.88	−4.17	3	−0.46
9	−0.074	3.91	−3.96	3	−0.95
10	−0.07	1.04	−4.49	2	−1.67
12	−0.36	4.30	−4.68	4	−0.39
13	−0.22	4.40	−4.59	4	−0.41
14	−0.038	3.78	−3.65	4	−0.38
15	−0.14	4.81	−4.90	2	−1.30
17[a]	NA	3.28	−3.28	3	−0.41
18	1.50	5.15	−5.16	3	−0.58
19[b]	−0.34	NA	−9.89	4	−0.55

V_{BL}: Viral load at baseline; V_{h4}: Viral load four hours after treatment initiation; V_{w1}: Viral load at the end of week 1; N: Number of measurements used to calculate slope for phase II; NA: Viral load measurement not available.
[a] V_{h4} was missing.
[b] Viral load at end of week 1 missing, so phase 1 slope was computed using viral load at the end of day 2.

virions *c* and by the efficacy, ε. The subsequent second-phase decline was predicted to mainly reflect the death/loss rate of productively infected cells. In the era of IFN-free all oral DAA therapy, the typical HCV decline is also biphasic (Dahari et al., 2011, 2016). In the current study, it is not possible to identify all viral kinetic parameters (t_0, c, ε and

Table 3
Individual model parameter estimates.

Participant Number	N	V_0 (log IU/ml)	t_0 (h)	ε	δ (d^{-1})	Predicted time to cure (d)	Δ (d)
2[a]	5	4.58	2.6	0.9941	0.420	36 [33–37]	6
4	6	5.36	4.1	0.9996	0.158	90 [83–92]	−48
8	5	5.18	3.4	0.9995	0.153	91 [84–94]	−49
9	6	6.82	4.8	0.9995	0.311	59 [54–60]	−17
10	5	5.97	14.6	0.9992	0.545	32 [29–33]	10
12	7	7.37	1.2	0.9999	0.138	128 [122–134]	−86
13	7	6.60	1.4	0 .9998	0.139	114 [106–117]	−72
14	7	5.96	2.4	0.9998	0.124	123 [114–126]	−81
15	5	6.11	2.6	0.9997	0.475	35 [33–37]	7
17	4	6.80	2.9	0.9988	0.135	141 [133–144]	−99
18	6	6.84	0	0.9999	0.288	58 [54–66]	−16
19	5	7.02	0	0.9999	0.038	377 [349–385]	−335

V_0, pre-treatment measured HCV RNA; N, number of HCV RNA measurements used for modeling; d, days; ε, therapy effectiveness; t_0: pharmacological delay (h = hours); δ, infected-cell loss rate; viral clearance was fixed c = 2 d^{-1}; [ ], min-max estimate of time to cure based on 5L and 20L of extracellular body fluid; **Δ**, difference between model-predicted time to cure and length of administered therapy (negative number indicates model recommends therapy longer than that administered).
[a] Participants who achieved SVR.

δ) due to lack of frequent viral sampling during the first phase of decline. Thus, we fixed the HCV clearance rate to c = 2/d based on the direct measurement of HCV half-life using linear regression. Interestingly, a previous modeling study (Osinusi et al., 2013) in chronic HCV-infected patients treated with SOF + R estimated a large range of c (1.88–7.15 d^{-1}), so it is not known whether the HCV half-life differs between individuals with chronic versus acute HCV infections.

Sofosbuvir plus ribavirin for 12–24 weeks was previously evaluated as a treatment for chronic genotype 1–3 HCV infection, with variable SVR rates which were high in genotype 2 [SVR at 12 weeks (SVR12): 88%–97%] and more modest in genotype 1 [SVR12: 68%–85%] and genotype 3 [SVR12: 56%–89%] infected patients. (Gane et al., 2013; Zeuzem et al., 2014; Molina et al., 2015; Sulkowski et al., 2014). However, since HCV kinetic analysis (or modeling) was not performed in these studies, the reason(s) for the different SVR rates under SOF + R is not known. In the current modeling study, most (n = 9) participants were genotype 1 with only three participants infected with genotype 3, precluding us from drawing conclusions as to whether viral kinetic parameters differ across genotype in recent HCV infections treated with SOF + R. Another major limitation of our study is that only one of the modeled individuals achieved SVR, and we were thus precluded from drawing conclusions about the model's positive predictive value for response to recent HCV infection under SOF + R therapy. Future studies of the treatment of patients with recent HCV infection with more potent DAAs will be needed to establish the positive predictive value of the model. For example, a pilot study of people with recent HCV infection treated with glecaprevir-pibrentasvir (GLE-PIB) for six weeks (TARGET3D Cohort 2, clinical trial number 02634008) demonstrated high efficacy (per-protocol SVR 96%; relapse, n = 1) (Martinello et al., 2019a). The high SVR suggested that some of these participants could have achieved cure in less than six weeks. Indeed, in a recent retrospective modeling of a cohort of chronically-infected patients (composed of treatment-naïve, treatment-experienced, cirrhotic, and non-cirrhotic participants) who received eight or 12 weeks of GLE-PIB, we found that 64% (28/44) might have been cured with less than seven weeks of the therapy, 50% in less than six weeks, and 16% in less than four weeks (Dasgupta et al., 2020). The findings suggest that modeling provides a means to identify chronically infected patients who would respond to a shorter duration therapy with GLE-PIB. Modeling could provide a similar advantage for recently infected participants treated with sofosbuvir/velpatasvir (Matthews et al., 2020).

In conclusion, modeling could be relevant to advancing a more individualized, response-guided approach to HCV treatment. Such an approach using early viral kinetic data (baseline, day 2, week 1 and/or 2 and week 4) has recently been implemented for the first time in a clinical setting for chronically-infected patients (Etzion et al., 2018). In the setting of recent HCV infection, where DAA regimens have yet to be standardized, response-guided therapy could provide great value.

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Authors contributions

Study concept and design: MM, GVM, HD. Acquisition of data: MM, TLA, GVM. Analysis and interpretation of data: EG, SD, KW, HD. Drafting of manuscript: EG, AC, SD, SLU, DB, SJC, HD. Critical revision of the manuscript for important intellectual content: MM, DY, OE, SJC, GVM, HD. Statistical and modeling analyses: EG, AC, SD, KW, DB, HD. Study supervision: HD.

Meeting procedures

The study was presented at the 70th Annual Meeting of the American Association for the study of Liver Diseases. Boston, MA, USA, Nov 8–12, 2019

Writing assistance

None.

Declaration of competing interest

GVM advises, is on the speakers' bureau, and received grants from Gilead. She is on the speakers' bureau and received grants from AbbVie and Bristol-Myers Squibb. She received grants from Janssen. HD has consulted for CoCrystal Inc. None of the other authors has any financial interest or conflict of interest related to this research.

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