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ORIGINAL RESEARCH

HCV Viral Load Greater Than 1000 IU/ml at Time of Virologic Failure in Direct-Acting Antiviral-Treated Patients

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ABSTRACT

Introduction: One of the remaining barriers to reaching WHO elimination targets of achieving global hepatitis C (HCV) cure is a lack of an established lower limit of detection (LLOD) to confirm cure post-treatment in near-patient technologies. Determining a LLOD at virologic failure aids in increasing testing feasibility through point-of-care assays in resource-limited settings.

Methods: We described the level of viremia in 69 patients experiencing virologic failure across 20 clinical trials (ENDURANCE-1, ENDURANCE-2, ENDURANCE-3, ENDURANCE-4, ENDURANCE 5–6, MAGELLAN-1, MAGELLAN-2, EXPEDITION-1, EXPEDITION-2, EXPEDITION-3, EXPEDITION-4, EXPEDITION-5, EXPEDITION-8, SURVEYOR-1, SURVEYOR-2, VOYAGE-1, VOYAGE-2, CERTAIN-1, CERTAIN-2 and APRI). These findings were categorized as on-treatment, post-treatment week (PTW) 4 or PTW12 failures.

Results: The mean HCV RNA level at baseline in the overall population of 5033 patients was 4,193,712 IU/ml ± 5,955,028 (6.2 $\log_{10}$ IU/ml ± 0.8) compared to 9,585,957 IU/ml ± 8,247,669 (6.8 $\log_{10}$ IU/ml ± 0.5) in 69 patients experiencing virologic failure by PTW12. The mean HCV RNA level at the time of virologic failure for all patients was 6,004,980 IU/ml ± 7,077,728 (6.4 $\log_{10}$ IU/ml ± 0.7). Twenty patients had on-treatment virologic failure with a mean HCV RNA level at the time of failure of 9,136,360 IU/ml ± 8,572,113 (6.7 $\log_{10}$ IU/ml ± 0.7), 36 patients had relapsed by PTW4 with a mean HCV RNA level at the time of relapse of 4,131,344 IU/ml ± 5,246,954 (6.3 $\log_{10}$ IU/ml ± 0.6), and 13 patients, who experienced relapse between PTW4 and PTW12, had a mean HCV RNA at relapse of 6,376,003 IU/ml ± 7,758,968 (6.3 $\log_{10}$ IU/ml ± 1.0).

Conclusions: At PTW12, 100% of virologic failures had an HCV RNA > 3.0 $\log_{10}$ IU/ml. The data are encouraging that with a LLOD of 3.0 $\log_{10}$ IU/ml, a point-of-care test could identify

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all treatment failures accurately; larger studies, including real-world data, are needed to confirm these findings.

Keywords: Direct-acting antivirals; HCV RNA; Hepatitis C virus; Virologic failure

Key Summary Points
Why carry out this study?
Aid in establishing the lower limit of detection (LLoD) in order to confirm for HCV cure.
Determining LLOD at virologic failure aids in increasing testing feasibility through point-of-care assays in resource-limited settings.
What was learned from the study?
At post-treatment week 12, 100% of virologic failures had an HCV RNA > 3.0 log10 IU/ml.
The data are encouraging that a point-of-care test with a LLOD of 3.0 log10 IU/ml would likely identify all treatment failures accurately.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13677418.

INTRODUCTION

Globally, there are approximately 71 million individuals infected with hepatitis C virus (HCV) [1]. The World Health Organization (WHO) initiated global elimination targets to help achieve HCV elimination by 2030 [1–3]. While the addition of direct-acting antiviral (DAA) treatment therapy has resulted in efficacy rates routinely exceeding 95% with favorable safety and tolerability profiles, a remaining barrier to HCV elimination is the limited access to medications and the limited ability of public health programs to confirm sustained virologic response (SVR), HCV cure, after treatment [4]. Currently, confirming SVR requires the use of nucleic acid amplification testing (NAAT) with complex procedures and reagents [5]. In many resource-limited settings, such technology is not readily available in close proximity to patients; consequently, many patients cannot obtain confirmation of HCV cure after treatment, resulting in an unknown infection status and whether the possibility of re-treatment is necessary [4, 6, 7]. Establishing a lower limit of detection (LLOD) in affordable, WHO prequalified, point-of-care assays to measure the presence of HCV viremia is needed for large-scale diagnosis and confirmation of cure, helping achieve WHO HCV elimination targets and reduce mortality [6, 8].

Typically, point-of-care assays do not include molecular amplification steps and are less sensitive than gold-standard, laboratory-based HCV NAAT [4]. Currently, for diagnostic point-of-care assays, a qualitative HCV RNA assay needs to have a LLOD of $\leq$ 1000 IU/ml (3.0 $\log_{10}$ IU/ml); however, there is limited evidence for the LLOD for assays testing for a cure [8]. Therefore, to establish LLOD in order to test for HCV cure via point-of-care assays, it is essential to characterize the level of viremia at the time of detecting HCV treatment failure to understand the sensitivity required to identify those who are not cured. Furthermore, it is important to identify the demographic and clinical correlates of those who have a low level of HCV viremia at the time of treatment failure, such that it is possible to make guidance for subpopulations that may not be appropriate for point-of-care testing.

The aim of this study is to describe population characteristics and the viral load at DAA failure to determine its implications for establishing LLOD at the time of SVR in simplified testing.

METHODS

In this descriptive analysis, we constructed a cohort of patients with HCV virologic failure, selected from the overall number of patients completing phase II and III clinical trials; no new patients were enrolled. All patients provided written, informed consent to participate in the previous studies; each study included in this analysis was consistent with the ethical guidelines of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. All previously conducted studies were approved at their respective sites by their independent ethics committee or institutional review board prior to enrollment. Inclusion criteria for this analysis were on-treatment HCV virologic failure or post-treatment HCV relapse. We defined on-treatment virologic failure as any one of the following: (1) confirmed increase in HCV RNA level of > 1 $\log_{10}$ IU/ml above the nadir during treatment, (2) confirmed HCV RNA level $\geq$ 100 IU/ml after the level had been $<$ 15 IU/ml during treatment or (3) an HCV RNA level $\geq$ 15 IU/ml at the end of treatment (EoT) (with at least 6 weeks of treatment) [9–19]. Some studies required two consecutive results [10–12, 18]. Post-treatment relapse was defined as a confirmed HCV RNA level $\geq$ 15 IU/ml between the EoT and 12 weeks after the last dose of trial drug among patients who had both completed treatment and had an HCV RNA of $<$ 15 IU/ml at the EoT [9, 13–19]. Plasma HCV RNA levels were determined by COBAS Ampliprep/Taqman® real-time reverse transcriptase polymerase-chain-reaction (RT-PCR) assay, v. 2.0 (Roche Molecular Diagnostics); two studies used COBAS TaqMan® RT-PCR assay v. 2.0 (Roche Molecular Diagnostics), where the lower limit of quantification (LLOQ) was 25 IU/ml [9, 10, 12–25]. In some studies, for patients receiving 12 weeks of glecaprevir/pibrentasvir (G/P) treatment, plasma HCV RNA levels were determined by using COBAS Ampliprep/Taqman® RT-PCR assay, v. 2.0, with a LLOD of 15 IU/ml, regardless of genotype (GT); in those studies, for patients receiving 8 weeks of G/P treatment, the COBAS TaqMan® RT-PCR assay v. 2.0 was used, which had a LLOQ of 25 IU/ml, regardless of GT. The LLOD was 5.6, 12, 3.7 and 20.4 IU/ml for HCV GT2 and GT4, 5 and 6, respectively [26, 27]. Patients were excluded from the study analysis if they did not achieve SVR12 for reasons other than virologic failure, such as treatment discontinuation or loss to follow-up.

Study Population

Patients were included from 20 phase II and phase III clinical trials including ENDURANCE-1 (NCT02604017), ENDURANCE-2 (NCT02640482), ENDURANCE-3 (NCT02640157), ENDURANCE-4 (NCT02636595), ENDURANCE 5–6 (NCT02966795), MAGELLAN-1 (NCT02446717), MAGELLAN-2 (NCT02692703), EXPEDITION-1 (NCT02642432), EXPEDITION-2 (NCT02738138), EXPEDITION-3 (NCT03219216), EXPEDITION-4 (NCT02651194), EXPEDITION-5 (NCT03069365), EXPEDITION-8 (NCT03089944), SURVEYOR-1 (NCT02243280), SURVEYOR-2 (NCT02243293), VOYAGE-1 (NCT03222583), VOYAGE-2 (NCT03235349), CERTAIN-1 (NCT02707952), CERTAIN-2 (NCT02723084) and APRI (NCT03212521). All patients had chronic HCV; HCV RNA $>$ 1000 IU/ml was required at baseline for screening [9, 21, 23, 28]. In certain studies, an HCV RNA $\geq$ 1000 IU/ml was required, and in one study, an HCV RNA $>$ 10,000 IU/ml was required at screening [10, 11, 13–15, 18, 19, 22, 24–27, 29, 30]. As per study protocols, patients were excluded from clinical trial participation if they had hepatitis B (HBV) co-infection or decompensated cirrhosis of the liver.

Statistical Analyses

The distribution of $\log_{10}$ HCV RNA level (IU/ml) at time of virologic failure was summarized by a histogram. Data were descriptive and summarized by means and standard deviations as well as medians and ranges (minimum and maximum), frequencies and percentages.

RESULTS

Overall Patient Population

Across 20 clinical trials, 5033 patients with chronic HCV infection were enrolled. HCV DAA therapy was administered for 8 weeks in 50% (n = 2539) of patients, 12 weeks in 47% (n = 2360) of patients and for 16 weeks in 3% (n = 134) of patients; 96% of all patients received G/P. Fifty-five percent (n = 2774) of patients were male, 62% (n = 3123) were white, and 31% (n = 1543) were Asian. The majority of patients were GT1 (47%, n = 2388), treatment-naïve (76%, n = 3843) and non-cirrhotic (80%, n = 4042). Most patients were human immunodeficiency virus (HIV) negative (95%, n = 3455). In the overall population, 26% (n = 1321) of patients were from the USA, 10% (n = 512) and 9% (n = 430) of patients were from China and Japan, respectively; 5% (n = 253) were from Korea. The remainder of patients were from 32 countries across North America, South America, Asia, Africa, Australia and Europe. Further baseline characteristics of the overall population are described in Table 1.

HCV RNA Levels in the Overall Population at Baseline

The mean (± standard deviation) HCV RNA level at baseline in the overall population was 4,193,712 IU/ml ± 5,955,028 (6.2 $\log_{10}$ IU/ml ± 0.8). The median HCV RNA level at baseline was 1,930,000 IU/ml [range 5.6 IU/ml–56,600,000 IU/ml] (6.3 $\log_{10}$ IU/ml, 0.8–7.8). Baseline HCV RNA levels were ≥ 2,000,000 IU/ml in 49% of patients, ≥ 1,000,000 IU/ml – < 2,000,000 IU/ml in 15% of patients and < 1,000,000 IU/ml in 36% of patients.

Patients Experiencing Virologic Failure

Of the 5033 patients enrolled across 20 phase II and phase III clinical trials, a total of 69 patients experienced virologic failure. Of those, 66 patients received G/P therapy for 8, 12 or 16 weeks and 3 patients received a DAA other

Table 1 Baseline demographics for the overall population

Characteristic	Overall N = 5033 n (%)
Male	2774 (55)
Race	
White	3123 (62)
Black or African American	291 (6)
Asian	1543 (31)
Age ≥ 65 years	888 (18)
BMI (kg/m^2) (median, range)	25.4 (14.2–65.7)
GT	
1	2388 (47)
2	1054 (21)
3	1140 (23)
4–6	451 (9)
Treatment-naïve	3843 (76)
IFN or SOF-based treatment experience	1014 (20)
DAA-based treatment experience	175 (4)
Country (≥ 5% of patient population)	
USA	1321 (26)
China	512 (10)
Japan	430 (8.5)
Korea, Republic of	253 (5)
Fibrosis score	
F0–F1	2972 (62)
F2	343 (7)
F3	497 (10)
F4	979 (20)
Baseline HCV RNA level (IU/ml) (mean, SD)	4,193,712 ± 5,955,028
Baseline HCV RNA level (IU/ml) (median, range)	1,930,000 (5.6–56,600,000)
< 1,000,000	1809 (36)
≥ 1,000,000—< 2,000,000	751 (15)
≥ 2,000,000	2473 (49)
Baseline HCV RNA level ($\log_{10}$ IU/ml) (mean, SD)	6.2 ± 0.8
Baseline HCV RNA ($\log_{10}$ IU/ml) (median, range)	6.3 (0.8–7.8)
HIV co-infection[a]	188 (5)
Recent injection drug Use[b]	66 (1)

Patients were excluded from clinical trials if they had comorbid HBV or decompensated cirrhosis

BMI body mass index, *DAA* direct-acting antiviral, *GT* genotype, *HBV* hepatitis B, *HIV* human immunodeficiency virus, *IFN* interferon, *SD* standard deviation, *SOF* sofosbuvir

[a] 1390 patients had missing HIV data

[b] Within the last 12 months

Table 2 Baseline demographics in patients with virologic failure

Characteristic	Virologic failure at PTW12 *N* = 69 *n* (%)
Male	51 (74)
Race	
White	45 (65)
Black or African American	1 (1)
Asian	23 (33)
Age ≥ 65 years	8 (12)
BMI (kg/m^2) (median, range)	25.1 (17.0–42.6)
GT	
1	17 (25)
2	7 (10)
3	42 (61)
4–6	3 (4)
Treatment-naïve	33 (48)
IFN or SOF-based treatment experience	23 (33)
DAA-based treatment experience	13 (19)
Country (≥ 5% of patient population)	
USA	21 (30)
China	13 (19)
New Zealand	8 (12)
Australia	7 (10)
Japan	6 (9)
Fibrosis score	
F0–F1	33 (49)
F2	9 (13)
F3	11 (16)
F4	14 (21)
Baseline HCV RNA level (IU/ml) (mean, SD)	9,585,957 ± 8,247,669
Baseline HCV RNA level (IU/ml) (median, range)	8,140,000 (135,000–36,100,000)
< 1,000,000	5 (7)
≥ 1,000,000— < 2,000,000	7 (10)
≥ 2,000,000	57 (83)
HCV RNA level (IU/ml) (median, range)	
On-treatment virologic failure[a]	7,425,000 (61,200–28,500,000)
Relapse by PTW12[b]	2,130,000 (7,040–27,900,000)
Relapse by PTW4[c]	1,780,000 (72,400–20,300,000)
Relapse between PTW4 and PTW12[d]	3,990,000 (7040–27,900,000)
All virologic failure subjects	3,350,000 (7040–28,500,000)
Baseline HCV RNA level ($\log_{10}$ IU/ml) (mean, SD)	6.8 ± 0.5
Baseline HCV RNA level ($\log_{10}$ IU/ml) (median, range)	6.9 (5.1–7.6)
HCV RNA level ($\log_{10}$ IU/ml) (median, range)	
On-treatment virologic failure[a]	6.9 (4.8–7.5)
Relapse by PTW12[b]	6.3 (3.8–7.4)
Relapse by PTW4[c]	6.3 (4.9–7.3)
Relapse between PTW4 and PTW12[d]	6.6 (3.8–7.4)
All virologic failure subjects	6.5 (3.8–7.5)
HIV co-infection[e]	1 (2)

Table 2 continued

Characteristic	Virologic failure at PTW12 *N* = 69 *n* (%)
Recent injection drug use[f]	1 (1)

Patients were excluded from clinical trials if they had comorbid HBV or decompensated cirrhosis

BMI body mass index, *DAA* direct-acting antiviral, *GT* genotype, *HBV* hepatitis B virus, *HIV* human immunodeficiency virus, *IFN* interferon, *PTW* post-treatment week, *SD* standard deviation, *SOF* sofosbuvir

[a] *N* = 20

[b] *N* = 49

[c] *N* = 36

[d] *N* = 13

[e] Twenty-one patients had missing HIV data

[f] Within the last 12 months

than G/P. Of the three patients who did not receive G/P treatment, one patient received treatment with sofosbuvir (SOF) + daclatasvir (DCV) for 12 weeks and two patients received treatment with SOF + ribavirin (RBV) for 12 weeks. Of the patients who received G/P and had virologic failure, 32% (*n* = 22) received 8 weeks of therapy, 48% (*n* = 33) received 12 weeks of therapy and 16% (*n* = 11) received therapy for 16 weeks. The majority of virologic failures were GT3 (n = 42, 61%) and GT1 (*n* = 17, 25%); 65% (*n* = 45) of patients were white and 33% (*n* = 23) were Asian. Ninety-eight percent (*n* = 47) of patients were negative for HIV; 21 patients had missing baseline HIV status. The majority of virologic failures were from the USA (*n* = 21, 30%), China (*n* = 13, 19%), New Zealand (*n* = 8, 12%) and Japan (*n* = 6, 9%). Further baseline characteristics of patients who experienced virologic failure are shown in Table 2.

HCV RNA Levels in Patients Experiencing Virologic Failure

The mean baseline HCV RNA level for all patients experiencing virologic failure by post-treatment week (PTW) 12 in an intention-to-

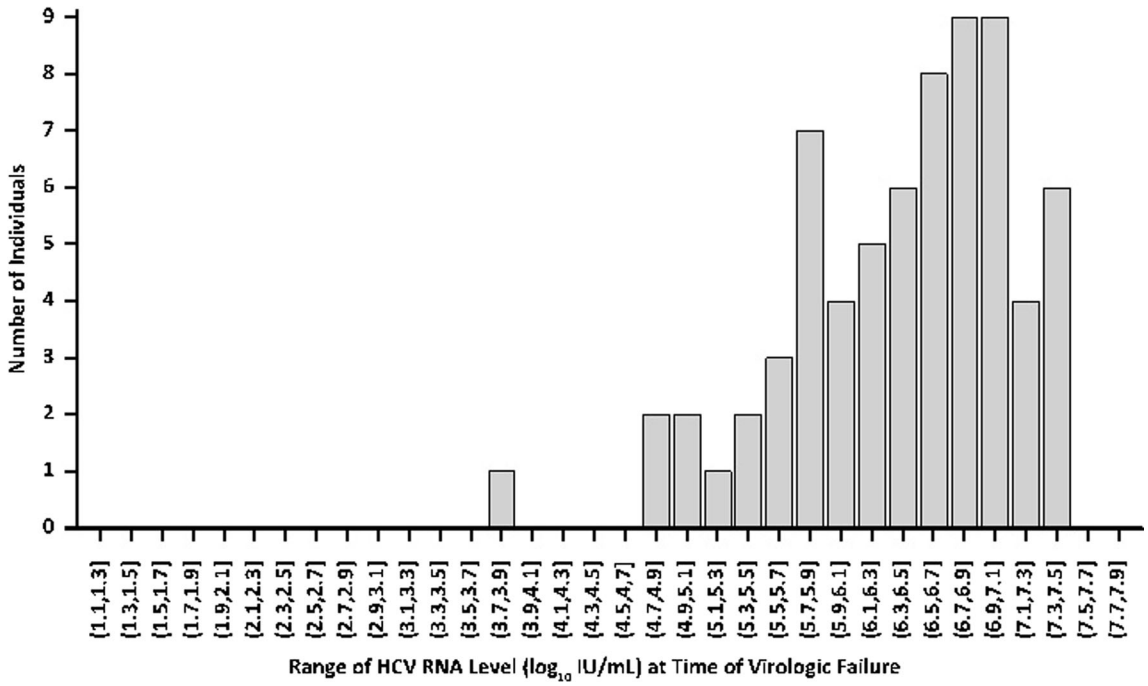

Fig. 1 Histogram of HCV RNA level (log10 IU/ml) at time of virologic failure (ITT population with virologic failure at PTW12) in 69 patients across 20 phase II/III clinical trials. *ITT* intention to treat, *PTW* post-treatment week

treat (ITT) population was 9,585,957 IU/ml ± 8,247,669 (6.8 $\log_{10}$ IU/ml ± 0.5). The mean HCV RNA level at the time of virologic failure for all patients was 6,004,980 IU/ml ± 7,077,728 (6.4 $\log_{10}$ IU/ml ± 0.7). The median baseline HCV RNA level was 8,140,000 IU/ml [135,000 IU/ml–36,100,000 IU/ml] (6.9 $\log_{10}$ IU/ml, 5.1–7.6). The median HCV RNA level at the time of virologic failure for all patients was 3,350,000 IU/ml [7,040 IU/ml–28,500,000 IU/ml] (6.5 $\log_{10}$ IU/ml, 3.8–7.5) (Fig. 1).

Out of the 69 patients who experienced virologic failure, 20 patients had on-treatment virologic failure with a mean HCV RNA level at the time of virologic failure of 9,136,360 IU/ml ± 8,572,113 (6.7 $\log_{10}$ IU/ml ± 0.7) and a median HCV RNA level at the time of virologic failure of 7,425,000 IU/ml [61,200 IU/ml–28,500,000 IU/ml] (6.9 $\log_{10}$ IU/ml, 4.8–7.5). Forty-nine patients experienced relapse by PTW12 with a mean HCV RNA level of 4,726,866 IU/ml ± 6,010,599 (6.3 $\log_{10}$ IU/ml ± 0.7). The median HCV RNA level of patients experiencing relapse by PTW12 was 2,130,000 IU/ml [7040 IU/ml–27,900,000 IU/ml] (6.3 $\log_{10}$ IU/ml, 3.8–7.4). The 36 patients who had a relapse by PTW4 had a mean HCV RNA level at the time of relapse of 4,131,344 IU/ml ± 5,246,954 (6.3 $\log_{10}$ IU/ml ± 0.6) and a median HCV RNA level at the time of relapse of 1,780,000 IU/ml [72,400 IU/ml–20,300,000 IU/ml] (6.3 $\log_{10}$ IU/ml, 4.9–7.3). There were 13 patients who experienced relapse between PTW4 and PTW12; these patients had a mean HCV RNA at relapse of 6,376,003 IU/ml ± 7,758,968 (6.3 $\log_{10}$ IU/ml ± 1.0) and a median HCV RNA at relapse of 3,990,000 IU/ml [7040 IU/ml–27,900,000 IU/ml] (6.6 $\log_{10}$ IU/ml, 3.8–7.4).

DISCUSSION

We analyzed data from > 5000 patients treated for HCV with DAA therapies to identify 69 patients with either on-treatment virologic failure or post-treatment HCV relapse. We then characterized the degree of HCV viremia at the time of virologic failure to help inform the LLOD for HCV cure.

Patients who experienced on-treatment virologic failure had the highest mean HCV RNA levels at the time that treatment failure was identified (6.7 $\log_{10}$ IU/ml). Patients who relapsed by PTW4, by PTW12 or between PTW4 and PTW12 had a similar mean HCV RNA (6.3 $\log_{10}$ IU/ml) as patients who relapsed between PTW4 and PTW12 having 6,376,003 IU/ml compared to 4,131,344 IU/ml and 4,726,866 IU/ml in patients who relapsed by PTW4 and PTW12, respectively. Understanding the HCV RNA level at various time points of virologic failure can aid in determining the LLOD at SVR to check for HCV cure. In all cases, 100% of individuals with a detectable viral load had an HCV RNA > 3.0 $\log_{10}$ IU/ml. Because the general limit of detection of near-patient technologies is approximately 3.0 $\log_{10}$ IU/ml, these data are reassuring that while point-of-care testing for HCV viremia may have a lower sensitivity compared the gold standard RNA testing, it may still be sensitive enough to accurately identify nearly all treatment failures, whether HCV viremia is tested while the patient is on treatment or after treatment is complete [8].

There are limitations to this study. Most notably, these data are from randomized controlled trials and may not reflect clinical treatment experience in real-world settings [31]. Treatment adherence was very high in these clinical trial cohorts, and treatment failure reflects virologic breakthrough despite treatment, as opposed to non-adherence to medication therapy; additionally, re-infection was not explored in the context of this analysis. In the majority of clinical trials assessed, patients were excluded at the time of screening if they had a baseline HCV RNA ≤ 1000 IU/ml [10, 13–15, 18, 22, 24, 29, 30]. In another study looking at HCV RNA levels at the time of virologic failure, baseline and PTW12 HCV RNA levels were highly correlated; in patients with low baseline HCV RNA levels experiencing virologic failure, low baseline HCV RNA levels may be associated with low PTW12 HCV RNA levels [32]. The potential association of low-level viremia at baseline and low-level HCV

RNA at PTW12 raises the concern of potential misdiagnosis with a low-sensitivity point-of-care assay. However, with the high expected effectiveness rates of DAA therapy in patients with low baseline HCV RNA levels, the overall risk is likely minimal. The LLOD in the clinical trials varied at 3.7, 5.6, 12, 15 and 20.4 IU/ml depending on the HCV RNA assay used and patient GT; however, the variation in LLOD levels was not significant as the lower end of LLOD values was not explored for the purposes of this analysis. Additionally, all patients experiencing virologic failure had an HCV RNA level > 1000 IU/ml. Furthermore, while we characterized viral load for on-treatment failure as well as post-treatment relapse, these were distinct cohorts with one observation per failure. As there were no data available on individuals at multiple time points, we were unable to determine whether viral load changes from the on-treatment period to the post-treatment period in individual patients. The small number of patients who experienced on-treatment virologic failure or post-treatment relapse may limit both statistical power and generalizability of results to real-world populations.

CONCLUSION

We analyzed data from 20 clinical trials to characterize the level of HCV viremia at the time of treatment failure to inform the LLOD needed to monitor HCV cure after completion of treatment. The data are encouraging that a point-of-care test with a LLOD of 3.0 $\log_{10}$ IU/ml would likely identify all treatment failures accurately in a similar patient population. The reproducibility in other patient populations is yet to be determined, and a larger study combining data from multiple contexts, including real-world settings in underserved, global populations, is necessary to confirm these findings; however, these preliminary data are encouraging.

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Compliance with Ethics Guidelines. All patients provided written, informed consent to participate in the previous studies; each study

included in this analysis was consistent with the ethical guidelines of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. All previously conducted studies were approved at their respective sites by their independent ethics committee or institutional review board prior to enrollment.

Data Availability. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g., protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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