

TITLE:

Recommendations for standardized nomenclature and definitions of viral response in trials of HCV investigational agents

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ABBREVIATIONS:

Hepatitis C Drug Development Advisory Group (HCV DrAG)

Directly Acting Antivirals (DAA)

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The HCV DrAG is a group of experts from academia, industry (including pharmaceutical and diagnostic companies), regulatory agencies, and community advocacy involved in new HCV drug development supported by the Forum for Collaborative HIV Research and funded by a number of companies involved in HCV research (see below). The goals of the HCV DrAG are (1) to produce consensus recommendations for monitoring and testing HCV drug resistance or, in areas where there is not consensus, a description of major points of view, and (2) to provide scientific guidance that may facilitate discussions among all stakeholders in the drug development process to work toward standardized approaches for future drug development. This manuscript represents the work of the Definitions/Nomenclature Working Group, one of several working groups within the HCV DrAG. Additional information about the HCV DrAG can be found at www.hivforum.org.

Abstract

Outdated virologic response terms used at key trial time points in clinical trials with first generation direct acting antivirals plus pegylated interferon and ribavirin have failed to keep pace with HCV drug development. A more intuitive and flexible nomenclature capable of adapting to continuing advances in HCV drug development is needed. Assistance in standardization of the field was provided by members of the Hepatitis C Virus Drug Development Advisory Group, a project of the Forum for Collaborative HIV Research with participation from the American Association of Liver Diseases, European Association for the Study of Liver Diseases and the Infectious Diseases Society of America. Our proposed descriptive, virologic response nomenclature for key decision points in trials (with and without lead-in treatment) is based on assay-specified lower limit of quantitation cut-off. This allows responses to be categorized as either quantifiable or unquantifiable HCV RNA, with unquantifiable responses further divided based on whether target HCV RNA was detected or not detected. The unified reporting recommendations will facilitate interpretation of results across clinical trials and validation of new response guided time points. As time critical treatment parameters are shortened in HCV trials, the proposed nomenclature will greatly simplify and facilitate future adaptations of virologic response terms. Our proposed nomenclature will also be helpful in developing treatment guidelines for use in clinical practice.

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Recommendations for Hepatitis C Virus Clinical Trial Viral Response

Nomenclature and Definitions for Investigational HCV Agents

Introduction

HCV drug development is occurring at an unprecedented, rapid pace, with two direct acting antiviral (DAA) medications approved in 2011 in combination with pegylated interferon and ribavirin (PEG-IFN/RBV), and nearly 20 agents in phase 2 and/or 3 trials with or without PEG-IFN or RBV.¹ The terminology and definitions used in trials for virologic responses and classification of patients have evolved as treatments have improved. The therapeutic goal of HCV antiviral treatment remains cure of infection. This is captured by the surrogate marker “sustained virologic response” (SVR), defined as undetectable HCV RNA 12 weeks (SVR12), or 24 weeks (SVR 24) after treatment discontinuation. On-treatment virologic response categories have become important for evaluating and tailoring the therapeutic strategy and defining response-guided therapy (RGT).

Numerous terms to describe these earlier temporal virologic responses are currently in use (Table 1), though their precise definition in clinical trials is often inconsistent. Since combinations of HCV investigational agents are demonstrating much earlier on-treatment viral suppression than the current standard of care -- in some cases measured in days rather than weeks -- it is critical that trial terminology be adaptable to the changing treatment paradigms.^{2,3}

The HCV Drug Development Advisory Group (HCV DrAG), a project of the Forum for Collaborative HIV Research (Forum), together with experts from the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL) and the Infectious Diseases Society of America (IDSA), were asked to assist in the standardization of the field. Following the structure and composition of the Forum, the HCV DrAG is composed of representatives from the U.S. and European regulatory agencies, academia, patient advocates, and industry. The HCV DrAG and its working groups provide a

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uniquely unbiased forum for discussion and consensus building on drug development-related issues. Here we present the results of the HCV DrAG's Definitions and Nomenclature Working Group. Consistency and clarity in nomenclature will facilitate progress in clinical research by increasing the ability to interpret results across studies. This will also be helpful in developing treatment guidelines for use in clinical practice.

Nomenclature for Categorizing Virologic Response

Issue/Problem: In clinical trials and clinical practice, early predictors of long-term treatment outcomes, such as virologic response at weeks 4 and 12, are used to decide the course of subsequent treatment (referred to as *response-guided therapy*).⁴⁻⁹ Patients are classified depending on their treatment response, using terms such as Rapid Virological Response (RVR), partial Early Virological Response (pEVR) and complete Early Virological Response (cEVR). These terms were defined in the PEG-IFN/RBV era (see Table 1). New response terms such as very Rapid Virological Response (vRVR) and extended Rapid Virological Response (eRVR) are entering the lexicon as new investigational therapies, with or without PEG-IFN/RBV, are tested and new benchmarks for very early virologic responses are characterized.

For current triple combination (PEG-IFN/RBV and a DAA) therapies, RVR, defined as “undetectable” HCV RNA at week 4 (Table 1), is a key positive predictor of SVR for drugs that do not use a PEG-IFN/RBV lead-in.¹⁰ However, for drugs that use a 4-week PEG-IFN/RBV lead-in period, RVR is measured at week 8 of overall treatment, i.e. at week 4 of DAA administration.¹¹ Such inherent inconsistencies in how treatment response predictors are defined make extrapolation and comparisons between drugs, even from the same class (e.g. telaprevir and boceprevir), difficult, resulting in cumbersome and unintuitive terminology, and demand renewed attention.

To add to the confusion, virologic responses have been reported based on different HCV RNA endpoints, not all of them validated for the specific assay being used, including HCV RNA below the lower limit of quantitation (<LLOQ), HCV RNA “undetectable” or “target not detected”, and below the limit of detection (<LOD) of the molecular assay used in the trial. Of these, only the LLOQ is a validated parameter according to the specifications of the assay used

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in the trials.^{6, 7, 12, 13, 14} The LOD is not as reliable since it is an extrapolated estimate that can be influenced by specimen dependent or other variables. The problem is illustrated by the fact that different LOD values have been derived for the same assay in different settings. In addition, for any HCV RNA assay, values between LOD and zero can still result in HCV RNA detection with a statistical frequency. While traditionally, early achievement of undetectable HCV RNA during treatment has been used as a marker for assessing eligibility for response guided therapy (RGT), retrospective analyses of trial data from the two newly approved DAA treatments, telaprevir and boceprevir, demonstrated the need to be cautious in interpreting a “below LLOQ but detectable HCV RNA” result to be the same as “undetectable HCV RNA”.¹⁵

We recommend that the old treatment response terms used in trials which are based on the prior standard of care PEG-IFN/RBV be revised to simplify the nomenclature while increasing its flexibility, thereby allowing adaptation to regimens of various potencies with different response kinetics. New definitions being considered are designed to be as *descriptive as possible* and indicative of the *level* of viral load reduction. In the era of interferon-free regimens this intuitive nomenclature will provide trialists greater freedom to report virologic response data as seen in trials rather than through further adaptation of originally validated terms such as RVR, EVR, etc. Analysis of data obtained using the proposed nomenclature will greatly facilitate timely validation of key RGT time points for interferon-free HCV regimens.

Proposed Treatment Response Nomenclature

The HCV DrAG proposed nomenclature is based on virologic response by week of therapy and whether HCV RNA level is quantifiable using standard molecular assays. To achieve uniformity in the reporting of viral load assay results, the HCV DrAG recommends using the validated HCV RNA LLOQ rather than the statistically estimated LOD's or other values.¹⁶ The LOD cutoff value does not fall in the linear range, and is therefore inaccurate and not equal across patients. The LLOQ value is specific for each assay and represents the lowest HCV RNA concentration that is within the linear range of the assay. Therefore, the LLOQ is accurate and equal across patients. A “below LLOQ” result should be qualified as whether the HCV RNA target was detected (TD) or not detected (TND). It is important to emphasize that TD can be observed by a broad range of actual HCV RNA levels below the LLOQ.

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Viremia Unquantifiable (U): When the HCV RNA level is lower than the assay specified LLOQ for a particular time point of therapy, it is represented as, $W\#U_{TD/TND}$, where W# stands for week of treatment duration, U stands for Unquantifiable, and TD/TND notes whether target HCV RNA was detected or not detected. For example, treatment response for a patient with a week 2 viral load below LLOQ but where target HCV RNA was detected is designated as $W2U_{TD}$, while a week 4 viral load below LLOQ but where HCV RNA was not detected as $W4U_{TND}$, etc (Fig.1). When reporting viremia as unquantifiable, the specific assay's LLOQ should be clearly indicated.

In the context of PEG-IFN/RBV lead-in, $LI_{W/D}$ will stand for lead-in treatment, for W week(s) or D day(s). When viral load is below LLOQ, for a particular time point of therapy it is represented as $LI_{W/D}-W\#U_{TD/TND}$, where $LI_{W/D}$ stands for a particular duration of lead-in treatment, W# stands for the week of total treatment duration, U stands for unquantifiable and TD/TND notes whether the HCV RNA target was detected or not. For example, treatment response for a patient on boceprevir following a 4 week lead-in period with a week 8 viral load below LLOQ and where target was not detected will be designated, $LI_{4W}-W8U_{TND}$ (Fig. 2).

Viremia Quantifiable: If virus is quantifiable at any time during treatment, the \log_{10} decline in viral load from baseline should be recorded in increments of 0.1 \log_{10} . Baseline is defined as viral load at time of treatment initiation. Quantifiable HCV RNA measurements are represented as $W\#Q$ [\log_{10} decrease from baseline], where W# stands for week of treatment duration, Q stands for Quantifiable and \log_{10} decrease from baseline denotes the change in \log_{10} value from baseline. For example, a week 2 viral load decline of less than 1 \log_{10} from baseline is described as $W2Q[<-1.0]$ (see below); a 1.5 \log_{10} decline from baseline at week 4 is described as $W4Q[-1.5]$ (Fig. 3).

With lead-in ($LI_{W/D}$) treatment with PEG-IFN/RBV (described above), quantifiable viral load for a particular time point of therapy is represented as $LI_{W/D}-W\#Q$ [\log_{10} decrease from baseline], where W# stands for week of treatment duration and \log_{10} decrease from baseline stands for the

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\log_{10} value change from baseline. For example, treatment with a 4-week lead-in achieving a 2.3 \log_{10} decline from baseline at week 8 is described as $LI_{4W}-W8Q[-2.3]$ (Fig. 4).

Declines of less than 1 \log_{10} are reported as $W\#Q [<-1.0]$, where $W\#$ stands for week of treatment duration, Q stands for quantifiable viremia, and <-1.0 refers to a less than a 1.0 \log_{10} decrease of viral load from baseline. For example, a viral load decline from baseline of less than 1.0 \log_{10} at week 2 is represented as $W2Q [<-1.0]$ (Fig. 5).

Similarly, with treatment lead-in ($LI_{W/D}$), viral load declines of less than 1.0 \log_{10} should be reported as $LI_{W/D}-W\#Q [<-1.0]$, where $W\#$ stands for week of treatment duration, Q stands for quantifiable viremia, and <-1.0 refers to a less than a 1.0 \log_{10} decrease of HCV RNA from baseline. For example, following a 4-week lead-in, a viral load decline from baseline of less than 1.0 \log_{10} is represented as $LI_{4W}-W8Q [<-1.0]$ (Fig. 5).

As the time to critical response shortens, days (“D”) can be substituted for weeks (“W”) for future treatment regimens.

The terminology for a lead-in necessarily complicates the nomenclature. As trials investigate more potent and efficacious treatments it is likely that a lead-in treatment will no longer be required and that this part of the nomenclature can be eliminated.

For the purposes of familiarizing people with the proposed nomenclature, simultaneous use of both old and new nomenclature is recommended. For example, a 4-week unquantifiable HCV RNA result in a no lead-in scenario should be reported as $W4U_{TND}$ (RVR).

For currently approved therapies, response guided therapy (RGT) would be translated as follows:

RVR (Rapid Virologic Response) is currently defined as unquantifiable HCV RNA at week 4 of DAA therapy with target not detected. Based on the aforementioned nomenclature, it should be reported as $W4U_{TND}$ for no lead-in, and $LI_{4W}-W8U_{TND}$ with lead-in. Recently, several clinical trials have used a less strict definition of RVR that includes a week 4 value below LLOQ (not

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necessarily “undetectable”), and thus would be described as W4U in the protocol, but actual results reported as either W4U_{TD} or W4U_{TND} depending on the actual result.

eRVR (Extended RVR) is defined as unquantifiable HCV RNA at week 4 and through week 12 of therapy where target is not detected and should be reported as W4-12U_{TND}. If the week 4 cut-off is below LLOQ but target detected, then eRVR would be W4U_{TD}-12U_{TND}.

vRVR (Very Rapid Virological Response) is defined as unquantifiable HCV RNA with target not detected at week 2 after therapy initiation and should be reported as W2U_{TND}.

cEVR (Complete Early Virological Response) is defined as unquantifiable HCV RNA at week 12 of therapy where target is not detected should be reported as W12U_{TND}.

ETR (End of Treatment response) is defined as unquantifiable HCV RNA and target not detected at the end of treatment and should be reported as ETR_{TND}.

SVR12* (Sustained Virologic Response at week 12) is a new potential primary endpoint in DAA trials and is defined as unquantifiable HCV RNA and target not detected at 12 weeks *after* the completion of treatment and is reported as SVR12_{TND}.

SVR24* (Sustained Virologic Response) is the designation for unquantifiable HCV RNA and target not detected at least 24 weeks *after* treatment cessation and is reported as SVR24_{TND}.¹⁶

*If SVR12 and SVR24 HCV RNA assessments are unquantifiable, but detectable (e.g., SVR24U_{TD}), we recommend that the analysis be repeated before concluding the patient is cured.

Discussion

This is a watershed moment for the field of HCV therapeutic development. To ensure clarity within and between current and future HCV antiviral clinical trials, the adoption of consistent terminology is critical. These recommendations will bring much needed consistency to virologic response reporting in HCV clinical trials, which will ultimately benefit HCV clinical practices.

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A recent attempt by Jacobson et al¹⁷ also focuses on clarifying existing definitions and proposing new virologic response terms based largely on existing patient classification for treatment response. Jacobson's and our manuscripts propose virologic nomenclature that will bring simplicity and clarity to the field, and allow inter-trial comparisons, which will ultimately facilitate development of standardized treatment guidelines for clinical practice. The present proposal is more detailed and descriptive with respect to virologic nomenclature and is not based upon patient response categories¹⁷, but rather on the level of viral load reduction achieved. Ultimately, a new system of nomenclature is required that will lead to improved communication, standardization and clinical usefulness. We hope this is the first step in that direction.

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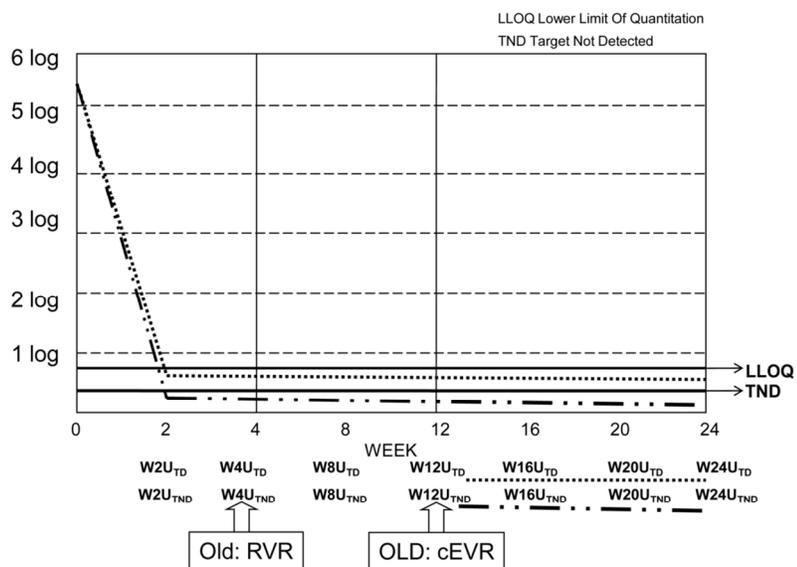
Table 1

HCV clinical trial treatment response terms

TREATMENT RESPONSE TERMS	DEFINITION	NEW NOMENCLATURE
vRVR: Very rapid virologic response	Undetectable HCV RNA after 14 days of treatment	W2U _{TND}
RVR: Rapid virologic response	Undetectable HCV RNA after 4 weeks of treatment	W4U _{TND} for no lead-in, and LI _{W/D} -W8U _{TND} with lead-in
eRVR: Extended rapid virologic response	Undetectable HCV RNA at week 4 <i>and</i> week 12 of treatment	W4-12U _{TND}
cEVR: Complete early virologic response	Undetectable HCV RNA after 12 weeks of treatment	W12U _{TND}
pEVR: Partial early virologic response	At least 2 log ₁₀ decrease in HCV RNA after 12 weeks of treatment	W12[-2]

Figure 1

Representation of quantifiable or unquantifiable HCV viremia



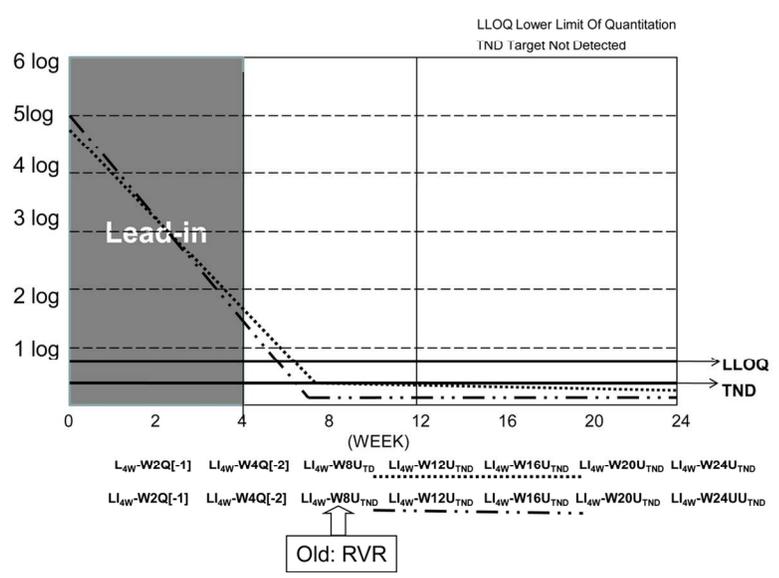
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Figure 2

Representation of quantifiable or unquantifiable HCV viremia in lead-in scenario

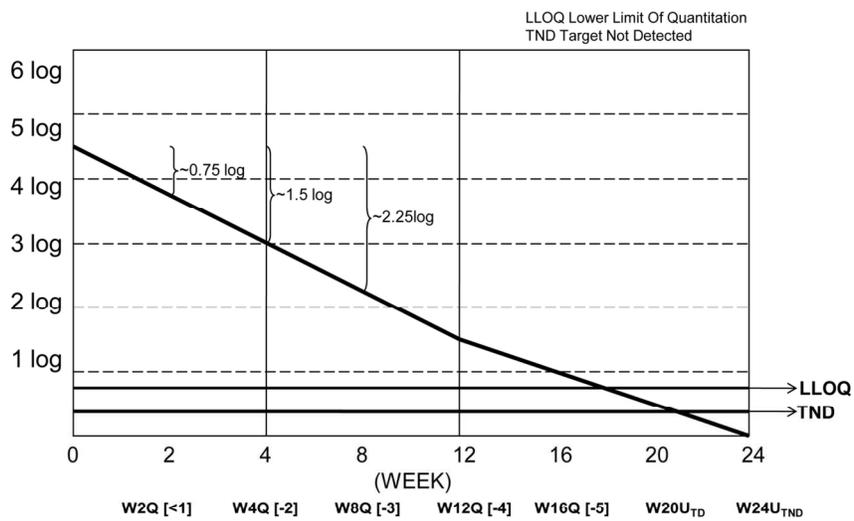


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Figure 3

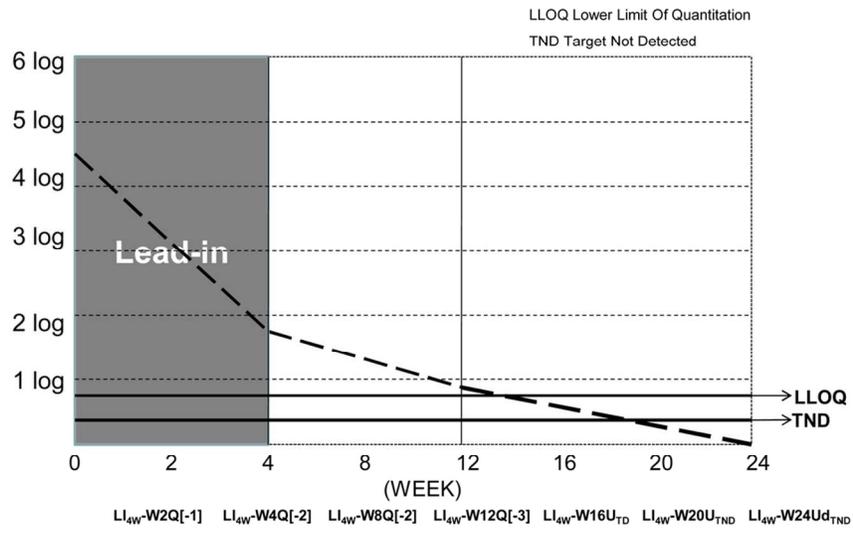
Representation of \log_{10} decline in HCV viremia

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Figure 4

Representation of \log_{10} decline in HCV viremia in lead-in scenario

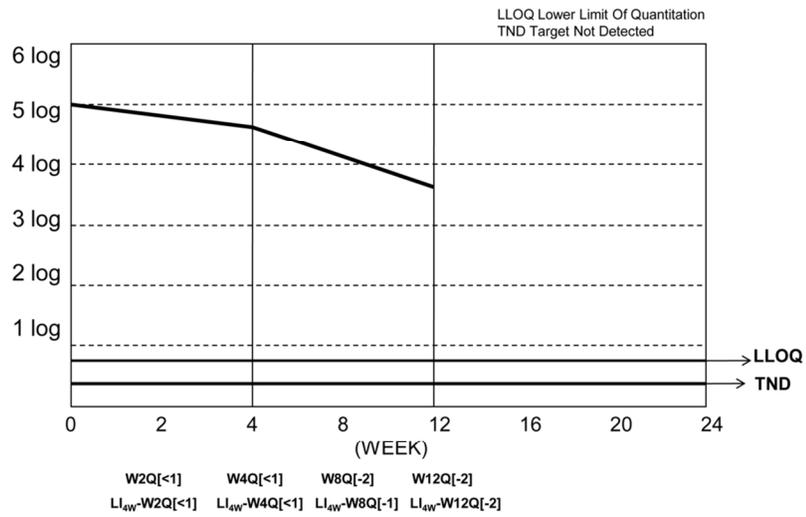


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Figure 5

Representation of $< 1 \log_{10}$ decline in HCV viremia in no lead-in (upper legend) and lead-in (lower legend) scenarios.



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