Finaly an important issue is the possibility to rechallenge patients after a first occurrence of immune-mediated hepatitis. The indication of a corticosteroid prophylaxis in this case remains debated. In two patients from Gauci *et al.*'s series and in three of our patients, immunotherapy was resumed without recurrence of hepatitis, suggesting that rechallenge is a feasible option.

At the moment several questions regarding IRAEs need to be addressed in the search for predictive biomarkers of toxicity, the precise pathophysiology, and the relationship between toxicity and antitumor response.[3,4] For liver immune related toxicity, further specific questions are to identify patients who can improve spontaneously, to search for the minimal effective dose of corticosteroids, and to identify the patients for whom immunotherapy can be safely reintroduced. Moreover, research should specifically focus on liver tissue biomarkers, which can better predict the liver severity of toxicity induced by immune-checkpoint inhibitors and would be of great value.

We hope that these preliminary data concerning the management of immune-mediated hepatitis will be a new starting point to re-think hepatic IRAEs, to make collective efforts in finding the answers to the above questions and to improve patient outcomes.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2018.04.019.

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Eleonora De Martin[1]
Jean-Marie Michot[2]
Stephane Champiat[2]
Olivier Lambotte[3]
Caroline Robert[4]
Aurelien Marabelle[2]
Catherine Guettier[5]
Didier Samuel[1,*]

[1]*AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire, INSERM, Unité 1193, Univ Paris-Sud, UMR-S 1193, Université Paris-Saclay, DHU Hepatinov, Villejuif, France*
[2]*Département d'innovation thérapeutique et d'Essais Précoces (DITEP), Institut Gustave-Roussy, Université Paris Saclay, Villejuif, France*
[3]*APHP Hôpital Bicêtre, Service de Médecine Interne et Immunologie Clinique, Université Paris Sud, CEA, DSV/iMETI, Division of Immunovirology, IDMIT, INSERM, U1184, Center for Immunology of Viral Infections and Autoimmune Diseases, Le Kremlin Bicêtre, France*
[4]*Dermatology Unit, Department of Medical Oncology, Gustave Roussy, Paris Sud University, Villejuif, France*
[5]*AP-HP Hôpital Bicêtre, Department of Pathology, Le Kremlin-Bicêtre, France, Univ Paris-Sud, UMR-S 1193, Université Paris-Saclay, France*
*Corresponding author. Address: AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire, Univ Paris-Sud, UMR-S 1193, Université Paris-Saclay Villejuif, DHU Hepatinov, France. Tel.: +33145593403.
*E-mail address*: didier.samuel@pbr.aphp.fr


# Real-world data on antiviral treatments for hepatitis C virus infections: Can we define intention to treat or per protocol analyses?

*To the Editor:*

We read with interest a recent study that used real-world (*i.e.* observational) data from the German Hepatitis C-Registry.[1] The 12-week sustained virologic response (SVR) was compared between 8- and 12-week regimens of ledipasvir/sofosbuvir. The authors used classifications of intention to treat (ITT) and per protocol to define eligibility of patients for their analyses.[1] One classification of ITT defined eligibility as patients who completed treatment with either the 8- or 12-week ledipasvir/sofosbuvir regimen (SVR ~85%). The second classification of ITT defined eligibility as patients who initiated and completed either the 8- or 12-week ledipasvir/sofosbuvir regimen (SVR ~95%). Per protocol defined eligibility as patients who initiated and completed treatment, adhered to treatment throughout the duration, and had SVR status assessed 12 weeks post-treatment completion (SVR ~98%). Nevertheless, such use of the terms ITT and per protocol have undue popularity in real-world studies of direct-acting antivirals (DAAs).[1–3]

ITT and per protocol are approaches for statistical analysis of randomized controlled trials (RCTs) and pertain to treatment status.[4] Neither approach is used to define eligibility and neither approach is directly applicable to real-world studies. ITT involves analyzing outcomes for RCT participants based on the treatment to which they were randomized, regardless of adherence to the allocated treatment.[4] ITT preserves the balance of known and unknown confounders between comparison groups

Keywords: Hepatitis C virus; Direct-acting antivirals; Observational; Real-world; Intention to treat; Per protocol.

(*i.e.* exchangeability), which is the key benefit of randomization for causal inference. In contrast, real-world studies have an inherent risk of confounding by indication, which no form of statistical adjustment can completely resolve.[5] Per protocol involves analyzing outcomes for participants based on adherence with the allocated treatment, which addresses the issue of treatment misclassification.[4] The potential reduction in treatment misclassification comes with the trade-off of breaking randomization; a per protocol analysis effectively converts the trial to a quasi-experimental study.[4]

The approach by Buggisch *et al.*[1] and others is incompatible with ITT or per protocol definitions and raises serious concerns about overestimated SVR in real-world studies. To facilitate awareness of biasing mechanisms, the four possible types of HCV-infected patients who initiated DAAs in any real-world study regardless of treatment duration are illustrated (Fig. 1). The distribution of these four patient types across regimens (*e.g.* 8- or 12-weeks) ultimately determines the observed SVR incidence. Given that we cannot rely on randomization to designate treatment status as in an RCT and the planned treatment duration (8 weeks or 12 weeks) was not recorded in the registry,[1] we must rely on exposure to treatment for eligibility. Treatment duration could have been modified based on an intermediate measure of response, which exacerbates the potential for confounding by indication. Nevertheless, we emphasize that all four patient types would be eligible for the analysis. Type 1 and 2 patients were followed through treatment completion and 12-week SVR assessment, and SVR was achieved by type 1 but not type 2 patients. Type 3 patients completed treatment, but the SVR status was unknown because of loss to follow-up (*e.g.* some barrier to care), whereas type 4 patients were lost to follow-up before completing treatment (*e.g.* side-effects or other reasons for discontinuation) and SVR status was also unknown. Buggisch *et al.*[1] excluded type 4 patients because of missing SVR status, but these patients were eligible albeit unlikely to achieve SVR. In addition, the main analyses (labeled "per protocol") excluded type 3 patients because of missing SVR status despite SVR being possible but unknown. Such exclusion relies on the unrealistic assumption that excluded cases were missing completely at random.[6] Non-random exclusion of patients based on outcome status leads to a selected population of patients who completed treatment and had a high probability of SVR. Even the lowest estimate of SVR reported in the study (85%) may be an overestimate.

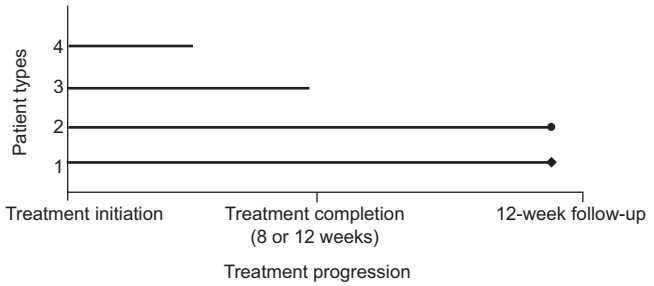


**Fig. 1. Distribution of patient types and follow-up in real-world studies of direct-acting antivirals for hepatitis C virus infections.** (The diamond at 12-week follow-up for patient type 1 represents sustained virologic response (SVR) and the circle for type 2 represents no SVR. Patient types without these symbols indicate loss to follow-up.)

Observational analogues of ITT and per protocol can be estimated using a counterfactual framework,[7,8] but these methods also require addressing the problem of missing outcome data. Given well-known problems with complete case analysis,[6] the challenge is how to handle patients with missing outcome data because of loss to follow-up. This challenge applies to RCTs and real-world studies, and no consensus has been established about the best approach. A simple approach is to designate worst-case and best-case scenarios, where none of the individuals with missing SVR status would have achieved SVR or all of the individuals would have achieved SVR, respectively.[9] The range of estimates based on these designations can be informative unless extensively missing SVR status is present.[9] More sophisticated approaches include multiple imputation and inverse probability weighting, but these approaches are not necessarily superior in all scenarios.[9,10]

We conclude that the interpretation of favorable response with 8- or 12-week treatment and the observed small differences between these regimens is problematic. Some limitations of real-world data cannot be overcome. Sensitivity analyses and cautious interpretation are encouraged.

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## Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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## Authors' contributions

RPO: Drafted the content. EWS: Critically revised the content.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2018.02.037.

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Rohit P. Ojha[1,2,*]
Ewout W. Steyerberg[3,4]
[1]*Center for Outcomes Research, JPS Health Network, Fort Worth, TX, USA*
[2]*Department of Biostatistics and Epidemiology, School of Public Health, UNT Health Science Center, Fort Worth, TX, USA*
[3]*Department of Public Health, Erasmus Medical Center, Rotterdam, Netherlands*
[4]*Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, Netherlands*
*Corresponding author. Address: Center for Outcomes Research, JPS Health Network, 1500 South Main Street, Fort Worth, TX 76104, USA. Fax: +1 817 702 6768.


# Reply to: "Real-world data on antiviral treatments for hepatitis C virus infections: Can we define intention to treat or per protocol analyses?"

*To the Editor:*

We thank Ojha and Steyerberg[1] for making a valid point regarding our manuscript. Indeed, defining analysis populations of real-life observational studies as intention-to-treat or per protocol is problematic, as this wording may suggest a higher comparability to clinical trials than exists.

In principle, even refined methods for adjusting confounders and minimizing bias cannot fully resolve the inherent problem of confounders in such trials. In our paper the wording (intention-to-treat and per protocol) was chosen for comparability with similar previous observational studies[2] and a lot of effort was made to make the definitions transparent by illustrating them in a figure and mentioning them several times in the article.

Furthermore, the results were carefully discussed and, overall, highly comparable with those from clinical trials. Therefore, potential overestimation of sustained response rates as illustrated and discussed in the letter by Ojha and Steyerberg seems to be a limited problem in our article discussing this real-world data.

## Conflict of interest

Peter Buggisch reports personal fees from AbbVie, BMS, Falk, Gilead, Janssen, Merz Pharma, and MSD outside the submitted work. Stefan Zeuzem reports personal fees from Abbvie, Bristol-Myers Squibb Co., Gilead, Merck & Co., and Janssen outside the submitted work.

## Supplementary data

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Peter Buggisch[1,*]
Stefan Zeuzem[2]
[1]*IFI-Institute for Interdisciplinary Medicine, Hamburg, Germany*
[2]*University Hospital Frankfurt, Frankfurt am Main, Germany*
*Corresponding author. Address: IFI-Institute, Lohmuehlenstrasse 5, 20099 Hamburg, Germany. Tel.: +49 4028407600; fax: +49 402840760253.
*E-mail address*: buggisch@ifi-medizin.de