Article details: 2017-0059	
Title	Real world treatment of hepatitis C with second generation direct acting antivirals (DAA): initial treatment results from a multicentre Canadian retrospective cohort of diverse patients
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Reviewer 1	Dr. Alnoor Ramji MD
Institution	Clinical Associate Professor of Medicine, Gastroenterology and Hepatology, Division of Gastroenterology, University Of British Columbia, Vancouver, BC
General comments (author response in bold)	Overall, this is an important study and one the largest reviews of DAA therapy from a centre in Canada. Remarkably good follow-up for a 'real-world' experience. I think is useful to have provided both ITT and mITT analysis. **Thank you for your comments. We provided both ITT and mITT analysis. We also clarified this in our methods and results.** Specific comments: 1. It would be useful to describe any differences in patient population between centres - e.g active IDU, OST patients. Further, was there any difference in patients lost to follow-up between centres (noted overall SVR same). **Only one participating site had patients with history of recent active IDU. Most of study subjects in the largest treating site (i.e., Calgary Liver Unit) did not have a history of recent IDU and were compliant with follow-up. It should also be noted that many of patients enrolled in this study representing special or marginalized populations had been followed for many years, and was only offered anti-HCV therapy when deemed overall stable and believed would be adherent to completing HCV treatment. Additionally, all treaters had dedicated multidisciplinary care providers helping with patient care and follow-up on therapy. Overall these factors contributed to the similar SVR and low rate of drop-out.** 2. HCC- The authors did comment on rate of de-novo HCC, what was the rate of HCC relapse. **There were no cases of HCC relapse in our study.** 3. GT3 – Please clarify results and add to the discussion section. Pg 10 of 30 line 13 –no significant difference in SVR between GT's; yet lower SVR in GT3 treated as per label with SOF/RBV. This is explained later, but this paper would read better and overall less confusing if had a paragraph dedicated to GT3 to explain all the results. The SVR rate in GT3 also varies based on fibrosis, and should be included here- how many persons with cirrhosis and what was their SVR compared to the NC cohort?. **Thank you we have clarified this in the results that the low SVR in Genotype 2 was due to the inferior regiment (SOF/RBV). We have also noted the number of cirrhotic vs non-cirrhotic cases.** 4. GT3: Pg 11 of 30 – other regimens mentioned but small numbers of patients which likely results in a NS SVR is 100% vs. 84.4% -can put in discussion. **Thank you. This is a good point and we clarified it in our discussion.** 5. GT3: Pg 11 of 30, line 23 – need to be specific when state small number of patients treated outside guidelines and had a lower SVR –is this the SOF/RBV (but was majority) or PRS – (which had 100% SVR). **Thank you, we have clarified this details on page 11, Line 235. This analysis was in reference to patients treated with sofosbuvir in combination with ribavirin. The clause "with sofosbuvir and ribavirin" has been added for clarification.** 4. Discuss why patients who were older had a lower SVR– analysis is conducted as a continuous variable. Why was data not analyzed per cohorts? This is important as the majority of persons are baby-boomers (and according to this will have significantly lower SVR). Atypical that in this study the maximum age is 64 years in a real-world setting? Why are older persons not included in this cohort? **Thank you. We agree that it is unusual that there were few older persons included in this real-world cohort. However, it is our general observation that there are relatively few older HCV patients seen in Calgary (i.e., age 65 and older). We wonder whether this reflects provincial demographics. The 2016 Canadian census data show that the median age of Albertans is lower compared to the rest of Canada, other than the territories (i.e., 12.3% age 65 and older in Alberta compared to 18.3% in BC and 16.4 % in Ontario).** **https://www.theglobeandmail.com/news/national/census-2016-statscan/article34882462/.** 5. SVR by regimen -8 vs 12 weeks: Authors comment that persons treated according to guidelines- does this also include prolonging regimens specifically in those who meet criteria for shorter course (8 weeks) of therapy? Ie meet guidelines for 8 weeks, but are treated for 12 weeks – did this occur and in how many persons? Further, if treated for 12 weeks ie. Overtreated- is this considered outside SOC? **Thank you. We have determined that X patients were "over-treated" for 12 weeks instead of the recommended 8 weeks. We would not consider this outside SOC since expert guidelines may suggest treating for 8-12 weeks at physician discretion.** 5. Any resistance data in those persons who failed their DAA regimen? Presume all failures were relapses though should state specifically if breakthrough vs relapse. **Thank you. In some patients who failed regimens the treating physicians did request resistance testing however this data is not available for this study.**
Reviewer 2	Dr. Lisa Barrett MD PhD
Institution	Assistant Professor, Infectious Disease/Microbiology and Immunology, Dalhousie University; Nova Scotia Health Authority, Halifax, NS
General comments (author response in bold)	Summary: This is a retrospective descriptive cohort study of DAA-based HCV treatment in 4 Canadian centers. It highlights response rates to treatment in both academic and community based settings with Health Canada approved product inserts as the standard of care. In general, real world data recapitulate the registrational results. Other North American data have already reported similar results, and while the information is not novel or unexpected, it does add to the body of available Canadian data that may be useful for Canadian policy makers. **Thank you we agree this is important. As noted above, the Canadian Task Foce on Preventative Care on HCV screening (CMAJ April 24, 2017 189:E594-E60) advised against Universal HCV screening, but these recommendations did not account for the availability of highly effective HCV regimens that have become more accessible for all**

patients with HCV infection regardless of fibrosis stage.

Comments and questions (all questions are suggested additions or revisions):

1. Material and Methods:
a) How was HCV chronicity defined?
It was defined as >6 months HCV antibody and HCV RNA positive.

b) Were all patients definitely beyond the acute phase?
Yes. Acute hepatitis C is relatively rare as most patients are asymptomatic and do not seek medical care. There were no cases of acute HCV included in the current study.

c) What was the ethnicity of the population? Were there a significant number of self-reported non-Caucasian or First Nations/Aboriginal people?
Thank you. Unfortunately, we did not systematically collect data on ethnicity in this study.

d) Is there a demographic difference in those HCV patients at these 4 clinics that were treated vs not (would speak to local and national generalizability of the data; also, add clarity on selection bias)?
Thank you, although ethnicity was not systematically collected based on available data, there was generally a higher proportion of First Nations and Canadian-born Caucasian patients seen at the CUPS and at SAC (HCV/HIV co-infection clinic).

e) HCC screening (how certain are we that new HCC is actually new? Did any of the cases miss screening before treatment?
Thank you. It is possible that some were new HCC cases, however most patients followed in our clinic undergo abdominal Ultrasound as standard of care for initial assessment pre-treatment.

f) TE measurements after treatment (called followup): what was the time range for these being done?
Most patients had TE completed ~6-12 months pre-treatment (to confirm eligibility for therapy) and at ~6- 12 months at the end of treatment. However, as noted a significant number of cases did not have follow-up TE performed.

g) Page 5, lines 43, 45: subscript 10 after the word log in each case
Thank you, this is corrected.

2. Results:
a) All abbreviations used in tables need to be defined including SVR. Be consistent about either SVR or SVR12 (outcome is listed as SVR12 and SVR is used interchangeably throughout the text and tables). Pick one.
Thank you, we agree that lack of consistency in abbreviations can be confusing and this is noted.

b) A further description of the 'type' of cirrhotics that failed therapy would be useful, given the discussion states that this result is different than registrational trials. I suspect these are 'worse' cirrhotics when they are primarily at a tertiary hepatology referral center with a transplant program. Can MELD scores of those that fail be compared? Or CPT score?
Most patients were Child-Pugh A cirrhotic, as the indications for therapy would exclude decompensated cirrhotic.

c) Page 9, line 23, sentence starting with 'although'; I'm unclear of the intent of the sentence.....perhaps remove 'although' and add the word 'and' after the p value?
Thank you, this is reworded for clarity.

d) Page 10, line 30: total of 362 vs 357 enrolled in the study. I assume some of the IFN were re-treated? Were they counted in both groups, if so? What about PrOD? Please clarify.
Thank you. We have clarified this in the methods.

e) Page 10, line 35: Was there a difference in the post-treatment timing of TE between those who did or did not achieve SVR, particularly in those with GT1a? Timing of the TE followup could significantly impact this result. How many patients were in this GT1a group with paired TE? What was the baseline TE of the paired TE group SVR vs non-SVR? Of the people who did NOT have paired TE, is there a difference in baseline TE cf to the group with paired TE? (i.e. is there a bias intrinsic to the paired TE group that would make these results non-generalizable?
Thank you. TE measurements are validated world-wide for assessment of liver fibrosis. Although many patients did not return for follow-up TE, the results of our study are consistent with the published literature and is generalizable.

f) The 8 vs 12 week data should be presented in a table if to be referenced later in the discussion (page 13, line 20). Highlight 8 week treatment SVR cf. ION-3.
Data analysis for SVR at 8 weeks were similar to SVR at 12 weeks. Therefore, we aimed to present our data consistently with previously published data on SVR 12.

g) Table 1:
a. Table column titles with the total number of SVR and not SVR should be changed. The total numbers should be the first line of the table NOT the title (confusing when you get to the rows that are sub-groups of each).
Table 1 has been changed.

b. Each percentage in each row should also have the absolute number
Thank you. This is a minor stylistic point we do not think this is necessary.

c. All the whole group rows should be at the beginning (for example, baseline HCV viral load, eGFR, previous treatment, liver transplant, MELD, and MELD-Na should come to the top of the table; after that, all rows that deal with sub groups should be listed). Having the subgroup rows interspersed with the entire group is confusing.
We think the current format has sufficient clarity. This is a minor stylistic point we do not think this is necessary.

d. Self reported / provider ascribed ethnicity should be included

	Thank you, we agree this information is important but unfortunately this data was not available. e. Percentage of individuals with detectable EOT VL should be added (or to a subsequent table) **Thank you. This information is not available.** h) Table 2: a. Table column titles with the total number of SVR and not SVR should be changed. The total numbers should be the first line of the table NOT the title (confusing when you get to the rows that are sub-groups of each). **Thank you. Table 2 has been re-formatted as recommended.** b. Remove trade name (Holkira) from line 26, 40, and 55. Use PrOD instead. **We have changed to the drug generic name.** c. In GT1a, I assume ribavirin was used? This should be noted. **This is noted.** d. Define abbreviations somewhere (eg. SOF, LDV, etc.) **These have been defined line 71, Page 4.** i) Supplementary table 1: a. Table column titles with the total number of SVR and not SVR should be changed. The total numbers should be the first line of the table NOT the title (confusing when you get to the rows that are sub-groups of each). **This table has been reformatted for clarity.** b. Treatment duration should be added with respect to guidelines **This information is noted.** 3. Discussion: a) Limitations of the retrospective data should be overtly discussion. Generalizability should be directly discussed – if the main reason these data are important is to provide 'Canadian data', an overt comparison to other Canadian provinces either currently or historically should be made – was there ever clinically important difference in previous response rates between provinces? Or between Canada and the US? **Thank you we agree this is an important point. To date there is no nationwide study comparing HCV treatment outcomes between Canadian provinces and territories or between Canada and the US. The Canadian Network on Hepatitis C (of which Calgary is a participating site) has prospective and retrospective ongoing study on HCV treatment outcomes that hopes to address this question.** b) Can the authors comment on the usefulness of EOT viral load and TE based on their experience (since both are mentioned in the text and can have important treatment, cost, and program implications)? **Both tests are useful to determine response to therapy and success of therapy. The recently published review (http://www.cochrane.org/CD012143/LIVER_direct-acting-antivirals-chronic-hepatitis-C) concluding that achieving an SVR is only a surrogate end-point and has no impact on HCV-related morbidity and mortality is highly controversial. A SVR indicates a clinical cure (clearance of serum HCV RNA) which is the main driver of ongoing liver injury. Thus, obtaining an end of treatment TE is a definitive clinical end-point – showing regression of liver fibrosis.** c) The discussion should be modified to reflect characterization of the cirrhotics as noted in the above comments on the results section. **Thank you.**
Reviewer 3	Ms. Alison D Marshall
Institution	The Kirby Institute, UNSW Sydney, Sydney, Australia
General comments (author response in bold)	Aspinall, A., and authors conducted a retrospective cohort study that assessed the real world treatment of hepatitis C infection with DAA therapies. Data was collected from four urban-based, healthcare centers in Calgary, Canada. The primary outcome of interest was SVR 12. Male sex, older age, and a history of hepatocellular carincoma (in genotype 1a patients) were independently associated with not achieving SVR. Further, there was no significant difference in SVR rates by clinic. Overall, study findings demonstrated that SVR rates were comparable to results found in clinical trials. The strengths of this paper are that it is well written and also, the subject matter is timely and contributes new knowledge to an area that is often overlooked. In agreement with the author(s), real-world treatment data with HCV DAAs are scarce, especially in Canada. **Thank you.** However, there are a few study limitations. 1. The manuscript is an appropriate length but I think would benefit from some additional detail, particularly in the Methods section. **We have provided additional details as per suggestions of Reviewer 1 and 2.** 2. I also think that the Introduction and Discussion section would benefit from some reference to the discrepancies between clinical trial data and real world treatment data. **Thank you. We have noted this in the introduction** 3. Given that this is a clinical journal (with a largely clinical audience) speaking more directly to the 'clinical implications' of the study findings in the Discussion I think would also be beneficial to readers. **We have highlighted the clinical significance of the data and targeted to a more general audience, as noted above.** 4. I think these changes can be made relatively easily but should (overall) be made concisely instead of adding substantial word count to the manuscript. **Agree.** Some suggestions for consideration are outlined below.

General comments
Introduction:
5. In the second paragraph, please consider making a brief statement as to why past evidence has demonstrated a discrepancy between clinical data and 'real-world data'. A possible study to reference is Saeed, S., et al. 2016: doi: 10.1093/cid/civ1222.
Thank you, this reference is added.

6. In the third paragraph, (following the sentence on real-world treatment data is lacking...) please consider making a brief statement as to how study findings on 'real-world' data will/could inform clinical practice. I think the Introduction could make a stronger rationale for why these studies are important.
Thank you. We have highlighted the importance especially given recent controversial publications (i.e. CMAJ CADTH recommendations and Cochrane Review, see above response to Reviewers 1 and 2).

Methods:
7. The Methods section does not specifically list the type of therapies reviewed. It is suggested that the list of therapies reviewed are listed (e.g. "Any patient that received..."). Alternatively, the authors could briefly state that, "IFN-based therapies were included because/if..." and list the "IFN-based therapies reviewed were..."
Thank you, this is noted.

8. The Methods section is an appropriate length. However, I think that this section could benefit from some additional detail that can be stated concisely. In particular, it might be helpful to outline some inclusion/exclusion criteria for the selection of patient files. Was information on why files were excluded recorded (e.g. not enough information on patient file)? If yes, please mention this. Please also see the Specific Comments for further suggested corrections.
This is clarified as noted above in response to Reviewer 1.

Discussion:
9. Please add a Limitations paragraph in the Discussion section. For instance, how are study findings generalizable/not generalizable to the greater population that has chronic HCV in Canada? Are there any study biases and if yes, how were these minimalized? The data will be limited by the type of information that was initially collected by the clinics/specialist centers. Further, how the information was collected (e.g. sampling technique) by the author(s) should be mentioned as a potential bias and also please mention how such biases were minimized.
Thank you. The authors speculated that the major difference between Alberta and other provinces is age group of our patients, as a reflection of the overall younger age demographic as well as immigrant population (Canadian Census 2016). As noted above in response to Reviewer 1, larger nationwide studies will be important to confirm this finding.

10. Further, would the same results have been expected with 4 other centers in Calgary? Who were not included in the results (e.g. people who inject drugs)? Similarly, persons with HCC are often excluded from clinical trials. I think that this should be mentioned briefly and also how study findings contribute new knowledge to this area.
We have noted this in the discussion.

11. Please consider briefly stating the main clinical implications of study findings. Please also make a statement about possible future research in this area (e.g. Long-term follow-up of persons who have achieved SVR?). Also, are there any other 'real world' treatment studies to compare to (in Canada)?
Thank you, this is noted in response to Reviewer 2 – there is ongoing prospective and retrospective data collection by Canadian Network on Hepatitis C that hopes to collect long-term follow-up data.

Specific comments
12. Title: Please consider listing the study design in the manuscript title.
Thank you. We prefer to keep the original title for this manuscript.

13. Title: Please consider changing the title to 'DAAs' as opposed to 'second-generation DAAs'. In its current form, the title is a bit misleading.
Thank you. We prefer to use the current title since we have published data on first-generation DAA's and would like to differentiate between the current study and our previously published work (O'Neil et at., Can J Infect Dis Med Microbiol. 2015 Nov-Dec; 26(6): 293–296).

Introduction:
14. (p. 4) Please consider removing: "Our data includes a diverse cohort of patients...novel treatment regimens." These two sentences seem to be out of place as the last sentences in the Introduction and do not seem to add anything to this section. These sentences could be moved to the Discussion section or removed entirely.
Thank you, we would prefer to emphasize the study significance up-front in the introduction.

15. (p.4) "Both regimens were included...in Alberta in 2015". Is there any reference for this? (e.g. a provincial government document or website link).
http://www.gilead.com/news/press-releases/2014/10/health-canada-issues-notice-of-compliance-for-gileads-harvoni-ledipasvirsofosbuvir-the-first-oncedaily-single-tablet-regimen-for-the-treatment-of-genotype-1-chronic-hepatitis-c
http://www.abbvie.ca/content/dam/abbviecorp/ca/en/docs/Press-Release-Holkira-Pak-CANADA.pdf

16. (p.4) Please consider spelling out acronyms first time used (e.g. United States). Also, please consider rephrasing 'longer period of time', which is subjective. As an example, provide the year when HCV DAAs became available in USA and/or European countries (e.g. France, Germany, etc.).
This is done.

Methods:
17. (p.4) "for all HCV patients who received antiviral therapy". Is there a timeframe that was decided prior to data collection (e.g. 2014-2016)? If yes, please state here. Were all patients that were treated before 2014 then excluded?
Yes - all patients before this time period were excluded.

18. (p.4) More information is needed about the sampling strategy. Was it by convenience sampling (and explain why; maybe it

	was convenience sampling because you did not have access to large number of patient records)? For example, Vassar and Holzmann (2013) provide some methodological considerations for chart reviews doi.org/10.3352/jeehp.2013.10.12 that might be helpful to refer to. **Thank you, we have amended out Methods section to reference our sample size and power calculations, this was a convenience sample.** 19. (p.4) Were these patients all receiving treatment through "reimbursed therapies" (i.e. patients did not pay out of pocket). This is not a crucial point but it does provide some idea of what patient data we are looking at. If not mentioned in the Methods, it should be mentioned as a potential limitation. **Thank you, Canada has Universal Health Care coverage and Alberta Health Care provides reimbursement for treatment of hepatitis C if > Stage 2 Fibrosis.** 20. (p.4) Was the data extraction from hospital/center client database? Or was there one centralized database? Is it possible to mention the name of this database? **This is outlined in the methods there were separate treatment and clinic databases at each participating site (i.e., Calgary Liver Unit, SAC and CUPS). Alberta has a province-wide EMR that is inclusive of clinical and diagnostic patient data.** 21. (p.4) Which study author(s) extracted the data? (p.4). What was the time period for data extraction? Was there a specific extraction form that used (paper format) or electronic format for extracting the data? **Data was extracted by several authors including AA, GSK, BS, GM, JK and CSC.** 22. (p.5) In terms of inclusion/exclusion criteria, did a patient have to have a TE score to be included in this study? **Yes. A TE score is needed to determine Fibrosis stage and eligibility for antiviral therapy.** 23. (p.5) Throughout the paper, genotype is listed as "genotype", "Genotype", and "GT". Please modify. **We have modified to be consistent.** 24. (p.5) Please make a brief statement to state why it was considered important to determine whether patients had been treated "within or outside Health Canada labeling". **This is important from policy makers and payer's perspective given the high cost of antiviral therapy it is important that physicians were following recommended treatment guidelines.** 25. (p.5) A possible option for the 'Standard of Care' section would be to put this information into a Table format. "We followed the Standard of Care for treatment of chronic hepatitis C infection in Canada as outlined in Table 1." **Thank you. We prefer to keep this information in a written section.** 26. (p.7) The paragraph concerning Study Variables could be made clearer with some slight modifications. Most of the study variables have been defined but I think for consistency, the authors should define all variables to increase clarity (e.g. baseline glomerular filtration rate, medical care centres). **We have attempted to define these variables instead of abbreviations for clarity. However, we expect that most of the readership will understand these variables.** 27. Please consider adding minimum age (presumably, this cohort does not include children); Please consider listing the HCV genotypes in brackets; Regarding previous HCV treatment, does this include whether someone was treated with interferon-based therapies or interferon-free therapies or is it just concerned with those patients that received interferon-based therapies (it might be of interest to readers if clients failed to achieve SVR with interferon-free HCV DAAs)? This might have been mentioned (and I missed it) but were only persons with chronic hepatitis C included in the study (or were persons with acute HCV infection included as well)? Whenever 'follow-up' is mentioned, please state the time of the follow-up (e.g. "liver stiffness…at baseline and 6 months follow-up"). This will help give the reader some idea as to expected 'liver stiffness progression' for the patient population over a certain time period. **We have clarified this in the Methods that only adult patients were included and we report our variables in the results that is consistent with previously published literature.** 28. (p.7) "histology by METAVIR score when available", would suggest that this information was not always provided. Please state how missing information was handled. **Most patients did not undergo liver biopsy. It is standard practice to rely on either liver histology or transient elastography (TE) for assessment of liver fibrosis.** 29. (p.4-7) Please consider briefly stating how the data was organized. Was author AA also the person that extracted, coded, and entered all data (into what program)? Also, was this task completed by one author (otherwise please consider recording how any inconsistencies were managed if two authors completed this task)? **Author AA reviewed the data after extraction. All the data was entered and extracted or coded into different clinic databases, or the provincial EMR was reviewed by co-authors as described above.** 30. (p.8) "Those who died had significant lower SVR rates". Would this not be expected? If this is a non-related treatment death, not sure that this needs to be reported? **Thank you. We think it is important to report any deaths in patients regardless of whether they achieved an SVR.** 31. (p.9) Please remove or modify the statement "all health care providers were considered local experts in HCV treatment". 'Local experts' is subjective. **We have modified this statement to clarify that all experts in hepatology or infectious diseases are permissioned to prescribe the DAA under Alberta Blue Cross pharmacare reimbursement program and have experience in treating HCV infection. This is noted on page 10, line 220.** 32. (p.10) "for the small number of patients with genotype 3 who were treated outside of established guidelines". Could you please consider restating the (n=) value here? Also, do we know what these individuals were treated with? If yes, please consider stating the therapies. **This number is provided.**

Statistical Analysis:
33. (p.7) Might want to briefly state how the final sample size was determined?
This is clarified above in response to the Editor and Reviewer 1, it was a convenience sample.

Results:
34. (p.11) "when the first Health Canada approved all oral regimen" became available. Please consider adding a reference.
This is referenced to the Alberta Blue Cross Pharmacare reimbursement website.

35. (p.11) "These observations are a departure from the findings of registration trials" Please restate references here.
This is noted.

Discussion:
36. (p.12) "Higher than expected SVR rates were seen in this group…" Please consider making a brief statement as to why this might have been the case.
We have added a brief statement.

37. (p.12) "We observed no differences in SVR between the four treatment centers…" Please provide a brief statement for why this might have occurred and/or if this result was anticipated.
We included both community vs. academic centres, thus it was important to compare SVR across the 4 treatment sites.

38. (p.13) "potential significant cost-savings". It is debatable whether a reduction in length of therapy will reduce cost of therapies. If this sentence remains in the document, please consider adding a reference.
This is noted.

39. (p.13) "de novo HCC in up to 6 months of follow-up after therapy". It would be beneficial if the '6 months follow-up' was stated in the Study Variables. Similarly, a bit of caution is warranted in this Discussion paragraph about HCC and SVR in that there needs to be sensitivity in suggesting causation between SVR and HCC, when an individual may have had a pre-existing HCC condition.
Thank you, this is noted.

40. The study authors make reference throughout the paper to the 'diverse' cohort (and could be viewed as subjective). Please consider stating how the cohort is 'diverse' and the implications of this. For example, it might help in the Methods section to briefly state how many 'vulnerable' people are serviced by the 'Calgary Urban Project Society'.
Thank you this is noted. According to CUPS website, around 5,000 patient are seen each year for a variety of health issues (online reference: http://cupscalgary.com).

41. (p.14) Please remove the sentence about "relevance of EOT viral load testing". The study findings do not contribute to this and also, this is already well-documented. Similarly, the main focus of the study was not 'highlights risk factors' (and this could also be removed). "In a largely HCV mono-infected population in Calgary, Canada, study findings demonstrated that real-world treatment data was comparable to that found in clinical trials…"
Thank you. This comment is noted.

42. (p.14) "we did not observe any cases of hepatitis B virus reactivation". This is based on one patient? It might be clearer to state "In the one patient with chronic hepatitis B infection, there was no…" If there are any clinical implications of this, please briefly state this.
Thank you, we have reworded this sentence as recommended.

43. Tables (all Tables). The information provided in the Tables could be made clearer and 'stand on their own'. Please consider adding a supplementary table that includes the baseline characteristics of the patients or add this information to an already existing Table.
Thank you. All tables had legends and foot-notes to clarify the data.

• Please reformat the Tables so that the information fits on one page (there is too much spacing between Table columns and rows)
Thank you.
• Please state the measurement of 'Age' (mean or median). If using inter-quartile range, please state this in brackets as well
This is done.
• If possible, please state the site name of the centers (or at least, 'specialist center' 'community clinic')
The practice type is included.
• Please state the previous treatment received (could also use 'Treatment naïve' and 'Treatment experienced' categories)
This is done.
• Please remove the 'Holkira' brand name and list out the therapy combination
This is done.
• Please restate the 'follow-up period' (6 months?) for 'developed HCC in follow-up' and 'Mortality in follow-up period'.
This is done.
• Please restate what 'cirrhosis' was defined as "Cirrhosis (≥12.5 kPa)". Could also separate fibrosis by category (no/mild; moderate; severe; cirrhosis).
The definition of cirrhosis is restated. In general severity of cirrhosis is categorized by Child-Pugh Class or MELD score.
• Please state what measurement is listed in the brackets. For example, Fibroscan baseline (please mention if range or interquartile range is listed in the brackets).
This is done.

Table 2. This might be more visually appealing and easier to read if made into a Figure(s). Please state out the IFN-based therapy received or provide a footnote.
Thank you. We prefer to keep the Table presentation format.

Table 3 does not list the p values while Supplementary Table 1 does. Please consider changing this to be consistent throughout.
In Table 3 we report univeraiate and multivariate adjusted odds ratio and do not need to provide p-values. The

	magnitude of correlation can be provided by the 95% CI.