Author’s response to reviews

Title: Effectiveness of Direct-Acting Antiviral Therapy for Hepatitis C in Difficult-to-Treat Patients in a Safety-Net Health System: A Retrospective Cohort Study

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Author’s response to reviews:

Dear Dr Recchioni,

Thank you for considering our manuscript (BMED-D-17-01172) entitled “Effectiveness of Direct-Acting Antiviral Therapy for Hepatitis C in Difficult-to-Treat Patients in a Safety-Net Health System: A Retrospective Cohort Study” for publication in BMC Medicine. We appreciate the careful reviews and helpful suggestions for revising our manuscript. We provide our responses to the comments below (in red). Two versions of the manuscript (clean and marked) are submitted as separate files.
Reviewers’ Comments:

Reviewer #1: The manuscript provides interesting insights into a (successful) treatment program for hepatitis C in mainly indigent in Dallas, Texas. The report and analysis is straightforward, credible and refreshingly brief. It is commendable that they were able to achieve such good treatment success in this hard-to-treat population, and so the description of how the clinic works in the Methods (and in the Discussion) is quite helpful.

One main question: can the authors indicate how many qualified for treatment but were not treated? And why? (not covered, active substance use, etc)

Authors’ response: Unfortunately, our database consists only of patients who initiated treatment in our clinic and therefore precludes this analysis. Regardless, from our gathered experience we can state that patients who did not receive treatment included those who were denied medications by their insurance providers, those who presented for evaluation but were then lost to follow-up, and others who were deemed to have too short a projected life expectancy to benefit from HCV treatment. We did not have rigid exclusion criteria for treatment.

Other suggestions for change are mainly discretionary, and mainly relate to Tables 1 and 2. In Table 1, readers would appreciate seeing the SVR rates for each of the groups listed, especially by treatment regimen; this entails additional column (columns) and if cell sizes are too small for analysis (eg those receiving EBR+GZR) that can be noted. Incidentally all abbreviations in the Table, such as drug abbreviations need to be spelled out in footnote.

Authors’ response: At the reviewer’s suggestion we have added SVR rates for each listed group to Table 1 and have added explanations of all abbreviations used to the table footnote.

In Table 2 it helps to see the N's in the analysis --eg 56 with decompensated cirrhosis.

Authors’ response: We have added the “N’s” to Table 2 as suggested.

In the Abstract, please indicate that the "SVR...significantly lower in patients with decompensated cirrhosis" was 82.1%.

Authors’ response: We have added that the SVR rate in decompensated cirrhosis was 82% (Line 37 of revised clean manuscript).
Reviewer #2: This is much needed study on underinsured and uninsured population.

1. The caveats include this is a retrospective analysis and without control.

Authors’ response: We thank the reviewer for their encouraging comments. We agree that our study is limited by the lack of control and its retrospective nature; we describe this in the discussion (Lines 301-303 of revised clean manuscript) but hope that, regardless, our results may be of interest to readers and in particular clinicians seeking to adopt a similar model of outpatient care in resource-limited settings.

2. I do have an issue with reporting primary outcome not as ITT. Why don't you report SVR of all patients and not on those who you have data?

Authors’ response: We agree with the reviewer that reporting intention-to-treat data may be a better reflection of treatment success in our population and have therefore modified our manuscript to report this as the primary outcome (Lines 35-36, 175-176, and 217 of revised clean manuscript).

3. Please indicate whether IRB approval was obtained for the study or not

Authors’ response: IRB approval was obtained for the study. We have detailed this in the methods section of the manuscript (Lines 100-101 of revised clean manuscript).

4. Please correct that decompensated cirrhosis was a "negative" predictor of SVR

Authors’ response: Per the reviewer’s recommendation we have corrected our phrasing to read that decompensated cirrhosis was a negative predictor of SVR (Lines 211, 221, 276 of revised clean manuscript).

5. Please note what "other" genotype represent?

Authors’ response: We grouped patients infected with HCV genotype 4, genotype 6, or having more than one genotype as having “other genotypes”. We have included clarification of the above in the footnote of Table 1.

6. How many HIV patients were on ART? Did you have to change Art prior to DAA therapy?
Authors’ response: All our HIV-infected patients were on ART. Of the 54 patients with HIV infection, 16 were made to change ART regimen prior to DAA therapy. We have included a brief description of this in the results section (Lines 163-165 of revised clean manuscript).

7. How was mental health disorder defined? Any DSM diagnosis?

Authors’ response: Mental health disorders were defined using ICD-10 criteria for schizophrenia, schizotypal, and delusional disorders (F20-29), mood (affective) disorders (F30-39), and neurotic, stress-related, and somatoform disorders (F40-48). We have included a detailed explanation of the above in the methods section (Lines 93-96 of revised clean manuscript).

8. How many had active SUD?

Authors’ response: Substance abuse was determined based on chart documentation of use of recreational drugs or ICD-10 codes indicating mental and behavioral disorders due to psychoactive substance abuse excluding tobacco (F11-16, 18, 19). Using these data extraction methods we were not able to distinguish active from prior history of substance abuse. Similarly, alcohol use was defined as a documented history of drinking more than 7 drinks per week for women and more than 14 drinks per week for men, or an ICD-10 diagnosis of alcohol related disorder (F10). We extracted the quantity of alcohol consumed by review of the “social history” tab in individual patient charts, under which providers document and update alcohol intake. Using these methods we were unable to distinguish between active and prior history of alcohol abuse. We have included our definitions of both substance and alcohol abuse in the methods section (Lines 96-100 of revised clean manuscript).

Reviewer #3: This is an excellent, well written and important paper - congratulations to all of you on both the work you've done and this paper describing it. I have a few suggestions:

1) A schematic of the model of care, and description would enhance the paper; you have demonstrated comparable SVR among populations described as "difficult to treat" -- a description of patient flow, or any lessons learned in delivery of care would advance the field.

Authors’ response: We thank the reviewer for their encouraging comments. At the reviewer’s suggestion we have included a schematic model that shows the flow of care from patient referral to assessment of treatment response (Figure 1). A further description of care is provided in the methods section (Lines 118-124 of revised clean manuscript). We gleaned many lessons from
our experiences and have included a brief description of these in the discussion (Lines 252-259 of revised clean manuscript).

2) Is this a mistake: "Similarly, rates of SVR were numerically but not significantly higher in patients with health insurance (90% vs. 90%, p=0.98)"?

Authors’ response: We thank the reviewer for identifying this error and have corrected our phrasing accordingly to state that there were no differences in SVR rates by insurance status (Lines 204-210 of revised clean manuscript).

3) Could you report on SVR among people with 'the' genotypes, especially G3 - I'm assuming that is why SOF/DAC was used - and perhaps a table with SVR by regimen? Not sure if there is room, but would be interesting to include in supplemental materials.

Authors’ response: At the reviewer’s suggestion we have reported on SVR rates among people with different HCV genotypes, including genotype 3, as well as SVR rates by treatment regimen (Table 1 of revised clean manuscript). We have also added a new table to be included as supplementary data that reports on the treatment regimens for different genotypes (Additional file 1).

4) WHO has updated their global estimate to 71 million chronically infected people rather than the 185 million; you may want to change this.

Authors’ response: We thank the reviewer for identifying this error and have corrected our report accordingly (Lines 46-47 of revised clean manuscript).

5) What happened with the rest of the patients who were screened- why weren't they treated?

Authors’ response: Unfortunately, this data is not available. Our database consists only of patients who initiated treatment in our clinic and therefore precludes this analysis. Please see response to Reviewer 1 (question 1) for further details.