Author's response to reviews

Title: Simeprevir with pegylated interferon alfa 2a plus ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a historical comparison

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Author's response to reviews: see over
First of all, we thank the reviewer for the time and effort spent to review our paper.

The authors attempt to investigate a clinically significant research question – specifically, to evaluate the efficacy of simeprevir+PegIFN#+RBV vs PegIFN#+RBV alone in HIV-1/HCV-coinfected patients. While the study’s methodology and statistics are sound, the use of a “non-adjusted indirect comparison” study design limits the strength of the authors’ findings and should be more clearly highlighted as a major limitation of this study.

We agree with the reviewer that in a historical comparison, bias from confounding factors (i.e. factors associated with the outcome of interest which differed between the different studies) might occur. As indicated by the reviewer, we have already discussed this limitation in the discussion section of our manuscript. In the revised version, we now state more clearly that this is a “major limitation” (page 12) and explain that “factors associated with the study outcome that differed between study C212 and the historical studies may have confounded the results”.

This is particularly significant given the substantial heterogeneity in the studies included in the meta-analysis, as noted by the authors. The authors do address study heterogeneity in part by using random effects modelling; however, they did not pursue additional testing or investigation of the underlying causes of the observed heterogeneity in order to provide a more concrete context for interpretation of study findings.

The main objective of the study was to compare the main results from study C212 with data from earlier (historical) studies that evaluated the efficacy and safety of PegIFNα-2a+RBV in patients with HCV-1/HIV coinfection. It was thus outside the scope of the study to identify potential predictors of response, e.g. within a meta-regression study. However, as superiority of simeprevir+PegIFNα-2a+RBV over PegIFNα-2a+RBV was also observed for all comparisons with the individual studies (excluding one study with N=10 participants), the identification of such factors was not considered of major importance within this study. We nevertheless agree with the reviewer that the reader should be aware of this limitation and now state this more clearly in the discussion section (page 12): “As no meta-regression analysis was performed, no conclusions regarding the impact of potential confounding factors on the outcomes of interest could be made.”

The authors briefly mention this as a potential limitation for their study design and described how sensitivity analyses were performed which supported their main analyses. However, only limited sensitivity analyses were performed – i.e. repeating analyses among trials that had same treatment duration or weight-adapted RBV dose as study C212. Other potentially important confounders that should have been investigated include proportion of patients with cirrhosis included in the studies (which was quite variable, ranging from 10 to 51% in the trials included) and proportion of treatment-experienced vs treatment-naïve patients (not available for most trials included).

As outlined above, one sensitivity analysis that is already reported in the paper focused on the comparison of study C212 with each individual historical study identified. As all these individual comparisons indicated superiority of simeprevir+PegIFNα-2a+RBV, additional sensitivity analyses were not considered as necessary: If the individual comparisons already show superiority of simeprevir+PegIFNα-2a+RBV, any combination of two or more of these individual studies within a meta-analysis (howsoever these were selected) will again indicate superiority of simeprevir+PegIFNα-2a+RBV. We thus feel that additional sensitivity analyses would actually not add important new information to what is already reported in the manuscript.
This article would be strengthened by providing more details on characteristics of the studies included and their patient populations: e.g. data on trial design (i.e. blinding/concealment, visit frequency, drop-out procedure), trial setting (geography, multicenter, etc), and other patient characteristics (i.e. baseline disease severity, control of HIV infection, HAART regimen used). By providing more information on how similar/dissimilar the patient populations were, this would at least allow readers to interpret the potential extent and direction of bias present.

As outlined above, the selection of studies based on any trial characteristic will not influence the overall conclusion regarding the superiority of simeprevir+PegIFNα-2a+RBV. However, we agree with the reviewer that additional information on trial characteristics might be helpful to evaluate trial heterogeneity. We thus have included now additional information on study region, trial setting (multicenter yes/no), study design incl. information on blinding in RCTs, and information on the proportion of patients on HIV therapy. We feel that the level of detail displayed in the updated table is sufficient to allow evaluation of the most important trial and patient characteristics while preserving readability of the table.