Author's response to reviews

Title: The French national prospective cohort of patients co-infected with HIV and HCV (ANRS CO13 HEPAVIH): Early findings, 2006-2010

Authors:

Marc-Arthur Loko (Marc-Arthur.Loko@isped.u-bordeaux2.fr)
Dominique Salmon (dominique.salmon@cch.aphp.fr)
Patrizia Carrieri (Pmcarrieri@aol.com)
Maria Winnock (maria.winnock@gmail.com)
Marion Mora (marion.mora@inserm.fr)
Laurence Merchadou (Laurence.Merchadou@isped.u-bordeaux2.fr)
Stéphanie Gillet (stephanie.gillet@isped.u-bordeaux2.fr)
Elodie Pambrun (Elodie.pambrun@isped.u-bordeaux2.fr)
Jean Delaune (jean.delaune@isped.u-bordeaux2.fr)
Marc-Antoine Valantin (marc-antoine.valantin@psl.ap-hop-paris.fr)
Isabelle Poizot Martin (isabelle.poizot@mail.ap-hm.fr)
Didier Neau (didier.neau@chu-bordeaux.fr)
Philippe Bonnard (philippe.bonnard@tnn.aphp.fr)
Eric Rosenthal (rosenthal.e@chu-nice.fr)
Karl Barange (barange.k@chu-toulouse.fr)
Philippe Morlat (philippe.morlat@chu-bordeaux.fr)
Karine Lacombe (karine.lacombe@sat.aphp.fr)
Anne Gervais (anne.gervais@bch.aphp.fr)
François Rouges (francois.rouges@avc.aphp.fr)
Alain Bicart See (abicart@hjd.asso.fr)
Caroline Lascoux-Combe (caroline.lascoux-combe@sls.aphp.fr)
Daniel Vittecoq (daniel.vittecoq@pbr.aphp.fr)
Cécile Goujard (cecel.goujard@bct.aphp.fr)
Claudine Duvivier (duvivier@pasteur.fr)
Bruno Spire (bruno.spire@inserm.fr)
Jacques Izopet (Izopet.j@chu-toulouse.fr)
Philippe Sogni (philippe.sogni@cch.aphp.fr)
Lawrence Serfaty (lawrence.serfaty@sat.aphp.fr)
Yves Benhamou (ybenhamou@teaser.fr)
Firouze Bani-Sadr (firouze.bani-sadr@tnn.aphp.fr)
François Dabis (francois.dabis@gmail.com)

Version: 4 Date: 15 September 2010

Author's response to reviews: see over
Dear Sir,

We appreciate the referees’ comments and feel confident that these comments will contribute to improve the quality of our manuscript. Modifications have been made in the revised manuscript (in red color) according to the reviewers’ suggestions and are detailed point-by-point in the following document.

Reviewer: 1

1/ There are some good longitudinal studies on factors associated to clinical progression of HIV-HCV coinfected patients that should be cited.

Answer # 1:
As suggested by the reviewer, four additional references have been mentioned in the introduction section of the revised manuscript (page 4, line 21, references #14-17 of the revised list of references).

2/ It should be specified if enrolled patients were those consecutively seen in each centre during the enrolment period that gave their informed consent to the inclusion in the cohort.

Answer # 2:
We agree with the reviewer that this point should be specified.
Patients included in our cohort were those consecutively seen in each participating centre and who fulfilled the inclusion criteria. This is now mentioned in the methods section (page 5, paragraph “inclusion criteria”).

3/ The number of included patients with SVR was established a priori or it was casual?

Answer # 3:
This figure represents the total number of patients with SVR, included in each centre during enrolment period and who agreed to participate. This is now highlighted in the methods section (page 5, paragraph “inclusion criteria”)

4/ The quality criteria of Liver Biopsy (6 portal tracts) is insufficient to accurately diagnose cirrhosis. According to this criteria an underestimation of the stage of liver disease in biopsied patients is highly probable given the hierarchical algorithm that has been described. However biopsied patients are a minority and this cannot heavily influence patients’ classification

Answer # 4:
We totally agree with the reviewer’s comment. The main limitation of the cirrhosis algorithm could be the quality criterion of liver biopsy. However, as pointed out by the reviewer, only 196 patients had a liver biopsy in the year preceding or following the enrolment in our cohort. In addition, the diagnosis of cirrhosis by the algorithm, based on liver biopsy only was approximately 10% of all these diagnoses. Finally, given the hierarchical dimension of this algorithm, patients inaccurately diagnosed by liver biopsy are likely to have been correctly diagnosed by the other tests used in the algorithm. Thus, this limitation could not influence patients’ classification.

5/ The rate of SVR is very low (40/238: 17%); SVR data should be stratified according to treatment received ( IFN monotherapy, PEGIFN monotherapy, IFN + R, PEGIFN + R) and when it was known by HCV genotype.
Answer # 5:
The stratification of SVR according to treatment received, as suggested by the reviewers is not applicable here as it was already mentioned in the manuscript (page 10, line 19) that the 238 patients treated for HCV since enrolment in the cohort, received peginterferon plus ribavirin. However, as suggested by the reviewers, the SVR has been stratified according to HCV genotypes. SVR was 20% in patients with genotype 1, 62% in patients with genotype 2 or 3 and 36% in patients with genotype 4. This is now mentioned in the results section (page 10, line 26).

6/ Follow up data are very interesting even if the duration of median follow up is short ( < 18 months). Given the usage of several methods to identify “cirrhotics” the predictive value of the algorithm and of each single test on the occurrence of HCV related severe events could be identified. This is very important information for clinical practice

Answer # 6:
We agree with the reviewer’s comment. The predictive values of the algorithm and of liver biopsy, Fibroscan and Fibrotest on the occurrence of HCV-related severe events have indeed been calculated. Overall, the negative predictive value of the algorithm and of each single test was good (98-99%), but the positive predictive values were low. These results are shown in page 12 (line 5) and in table 2 of the revised manuscript.

7/ As a general comment the discussion on the characteristics of the cohort could be shortened and a discussion on follow up data could be included

Answer # 7:
As suggested, the discussion on the characteristics of patients has been shortened. The paragraph on the discussion of the results of non-invasive tests has been suppressed (page 13, lines 17-23 of the original manuscript), and a paragraph on follow-up data has been added (page 14, lines 10-27 of the revised manuscript).
Reviewer: 2

1/ In publishing this cohort description at this point (while it appears the first true study from the cohort is still in press – reference 22), the authors do state that their goal is in part to allow the cohort subjects to understand the nature of the research conducted – which is a noble goal. On the other hand, it seems they already have the data in hand to report on some of the other elements they plan to publish (such as risk factors for response/non-response to HCV therapy among the group) which likely will provide some more interesting or novel information than does this descriptive study

Answer #1

We agree with the reviewer’s comment that more findings should be made available in near future. In addition to this descriptive study that allows an easy access to key characteristics of the cohort, specific analyses have been conducted in accordance with the objectives of the cohort and are being submitted to scientific journals.

2/ While the analysis of subjects who achieved liver-related endpoints does not present new information (that cirrhotics/those with lower cd4 are more likely to have liver related outcomes than non-cirrhotics) the analysis for other risk factors present within this large population is interesting and potentially could be highlighted more within the paper/abstract (rather than just the overall rate of HCV-related severe events).

Answer #2

As suggested, the results on the analysis of risk factors for HCV-related severe events have been more highlighted in the abstract and in the results section (page 11, from line 24).

3/ Would provide references for the WHO QOL index and the CES-D depression index used in table 1

Answer #3
As suggested, references for the WHO QOL index and the CES-D depression index have been mentioned in the revised manuscript (pages 7 and 8; references #24, 26 of the revised list of references).

4/ Would be useful in the discussion for the authors to describe the limitations of the cirrhosis algorithm (which could overcall the prevalence of cirrhosis within the cohort).

Answer #4
As suggested, the limitations of our cirrhosis algorithm have been discussed in the discussion section of the revised manuscript (page 14, line 21). See also answers #4 to reviewer #1.