



PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 39428

Title: Factors associated with DAA virological treatment failure and resistance-associated substitutions description in HIV/HCV coinfecting patients

Reviewer's code: 02544416

Reviewer's country: Serbia

Science editor: Fang-Fang Ji

Date sent for review: 2018-06-15

Date reviewed: 2018-06-21

Review time: 5 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input checked="" type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer's expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Minor revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This manuscript is well written. It describes Factors associated with virological failure and description of emergent resistant associated mutations in HIV/HCV coinfecting patients treated with DAA, which is certainly important for clinical practice. Sharing



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experience related to results of DAA treatment, especially in this specific group of patients is of great clinical importance. All parts of the manuscript are adequately written, methodology of the article is good, as well as presented results and discussion.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 39428

Title: Factors associated with DAA virological treatment failure and resistance-associated substitutions description in HIV/HCV coinfecting patients

Reviewer's code: 03644796

Reviewer's country: Singapore

Science editor: Fang-Fang Ji

Date sent for review: 2018-06-15

Date reviewed: 2018-06-22

Review time: 7 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer's expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Minor revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This is a French multi-center prospective hospital-based observational study of patients coinfecting with HIV and viral hepatitis C who received DAA therapy for HCV. The authors report that failure of all-oral DAA regimens occurred in 3.9% of patients, and



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RAS were found overall in 71% of patients failing DAA. A low platelet count was independently associated with virological failure. Major issues The paper is well-written, but like many other real-life studies, has several limitations, including the use of multiple DAA regimens with no randomization, patients of multiple genotypes, low number of patients with virologic failure, the absence of data for baseline RAS, most of which were discussed by the authors. Sanger sequencing assay was used for the detection of RAS, which may not be sensitive enough to detect minor populations of RAS (<15%). MELD (or MELD-Na) should be reported in Table 1 and evaluated as an independent variable in Table 2. Finally, some of the DAA regimens studied were from the previous generation (Daclatasvir, Simeprevir), and the results may not be entirely applicable to the newer, pangenotypic regimens. Minor problems 1. Use of short forms without full in the title: HIV, HCV, DAA. 2. P5 line11 cop/mL – Is it copies/mL? Please present in IU/mL. 3. P6 line 21 non virological – non-virological 4. P7 line 13 sub study – substudy 5. P8 line 21 sub-type-specific – subtype-specific 6. P10 line 3 Child Pugh – Child-Pugh 7. P12 line 5 inhibitor based – inhibitor-based

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[Y] No



PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 39428

Title: Factors associated with DAA virological treatment failure and resistance-associated substitutions description in HIV/HCV coinfecting patients

Reviewer's code: 03729295

Reviewer's country: Mali

Science editor: Fang-Fang Ji

Date sent for review: 2018-06-15

Date reviewed: 2018-06-22

Review time: 7 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	(General priority)	Peer-reviewer's expertise on the topic of the manuscript:
<input type="checkbox"/> Grade E: Do not publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Minor revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> General
		<input type="checkbox"/> Rejection	<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Dear authors, Your work could have been on a DAA virological failure and causes of failure (Basic study) focused on describing the characteristics of patients failing first-line DAA treatment in the real-life French nationwide ANRS CO13 HEPAVIH cohort of



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HIV/HCV coinfecting patients. Your manuscript looks like "ARRIVE Checklist". Accordingly, please receive reviewing comments in 14 main points: 1) Title: the title reflects the main subject and reader may readily understand the key concepts. However, we noticed proofreading for instance: "resistance" instead "resistant"; we also noticed in the title 19 words. It should be no more than 12 words. I would like to propose a title: "Factors associated with DAA virological failure and RAS description in HIV/HCV patients". Running title: "DAA failure in HIV/HCV coinfecting patients 2) The Abstract summarizes and reflects the work described in the manuscript. However, we noticed the study Aim is written as Background that contents "30 words" instead "20", because Aim requires no more than 20 words. The "method" does not describe sequencing analysis and adjustment for factors associated with risk of failure, while these informations are noticed in the "results"; we also noticed 60 words, while "method" requires no less than 80 words. In the "results" we noticed "HIV-RNA <50 cop/mL" that should be written "HIV-RNA <50 copies/mL". We noticed equally "conclusion" contents "36 words" more than "26 words as required by the Journal". I would have wished you consider these observations. 3) Key words: the key words reflect the focus of the manuscript to a degree. We noticed 4 keywords, while the Journal requires [5-10]; "HIV/HCV coinfection" is missing; the type of failure is not specified (like virological failure). I would have wished you consider these observations. 4) In the "introduction or Background section": sufficient background informations to provide the rational for the study are included, for instance: "Cure rates of over 90%, similar to those in HCV mono-infected patients, are described in clinical trial and real-life cohorts", "failures are often associated with the development of resistance-associated substitutions (RAS); However, emerging resistant strains appearing at viral rebound are a consequence rather than a cause of failure"; "In rare circumstances, especially for genotype 1a viruses, baseline mutations in the (NS5A) gene can preexist in the viral species before treatment introduction and may have a



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potentially deleterious impact on (SVR)", "Authors aimed to describe the characteristics of patients failing first-line DAA treatment in the real-life French nationwide ANRS CO13 HEPAVIH cohort of HIV/HCV patients", etc. 5) Method section: Experimental procedure enough well explained. The manuscript describes basic study design (ARRIVE check-list), adequate data collection and measurements described [data were collected prospectively by each participating center, using an eCRF; Virological failures were categorized; liver biopsy (METAVIR fibrosis stage F4), liver stiffness ≥ 12.5 kPa (FibroScan®; Echosens, France) and FibroTest® value ≥ 0.75 (Biopredictive, France); HCV resistance testing using automated sequencer (ABI-3500xL Dx) when HCV-RNA > 1000 IU/mL at sequencing time point], and Statistical data describing and analysis are done, etc. However, we noticed Sample size (or number of patients treated with DAA and included in the study is missing, whereas the results describe "877 patients treated with DAA-combination among them 559 subjects included in the analysis". In addition, the statement regarding "biostatistics review" is not noticed in "method section", but contributors' list related statistics analysis is noticed in "Acknowledgement section". I would have wished you consider these informations. 6) Results section: the research objectives are achieved by the experiments used in this study to a degree. Data related to the "characteristics of patients" and "viral response" are summarized in Table1; Adjusted logistic regression for factors associated with virological failure (Table2); RAS results in 14 patients with virological failure for whom sequencing was performed in routine (Table3). We remarked "Mean treatment duration" noticed in the "Abstract results" is missing in the "core results content" and the "method section" does not notice "mean" calculation. 7) Discussion section: Finding enough well interpreted and discussed with relevant literature. Study limitation enough well described, like "low number of subjects with virological failure, and thus, probably has limited power to identify all potential risk factors". Future direction and implications: "Among 7 patients



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with failure and interpretable pharmacological data, suboptimal blood concentrations of DAA were measured in 2 of them; these results could reflect different situations (drug interactions, suboptimal dosing errors, and suboptimal adherence) and warrant further investigation and wider-scale assessment of pharmacological data”, “high prevalence of non-structural-5A and -3 RAS at failure in the study confirms the EASL recommendation to evaluate, if resistance testing is available, HCV resistance to NS5A inhibitors (spanning amino acids 24 to 93) as these analyses can guide decisions for a further treatment”, etc. 8) Illustrations and tables: no figure is noticed, tables sufficient, good quality and appropriately illustrative of the paper contents. 9) Biostatistics: the manuscript describes Statistical data analysis in “Method section”, but the “method section” does not notice “mean” information, while “Mean treatment duration” noticed in the “Abstract results” is missing in the “core results content”. Statement regarding biostatistics review not noticed there, but contributors’ list related statistics analysis is noticed in “Acknowledgement section”. 10) Units: HCV-RNA : “copy or copies/mL” instead “cop/mL” 11) References: latest, important and authoritative references are cited in the manuscript. However, we noticed: - In “introduction section, line 4”: citation with more than 5 ref. [1-6] noticed; reference numbers regarding “superscript” and “no space”: line 5 “X[7-10]” instead “X [7-10]”,... - Manuscript Reference style does not meet journal requirement regarding “first authors’ name and volume number that should be typed in bold letters, journal title in abbreviated form and italic police. It should be matched with Journal format requirement. 12) Quality of manuscript organization and presentation: manuscript enough well, concisely and coherently organized and presented. However, we noticed that: - Police format and line spacing do not meet journal requirement: “Book Antiqua” instead “Arial”; Line spacing: “1.5” instead “2” and for References section “1.5” instead “1” - ORCID number and ARRIVE guideline statement are not noticed in title page of the manuscript. - Supported foundation (or



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funding) is stated after Acknowledgement. It should be stated in the first section of writing requirement. I would have wished you consider these observations. 13) Author prepared the manuscript according to the appropriate research methods and reporting, to a degree. 14) The ANRS CO13 HEPAVIH cohort, national multi-centre prospective hospital-based observational study of HIV/HCV patients, received approval by an Institutional Review board; Patients included in the cohort gave their consent for study participation. However, related formal ethics documents not provided by the Authors. Specific Comments To Authors Beside the above I would like to make important Specific Comments related your work as follows: 1. First: We noticed in your work: “no study to date has focused on HIV coinfection in the field”; “Similarities with previous studies like “low virological failure rate of 3.9%; low platelet count associated with a higher probability of DAA failure”. 2. Second: “high prevalence of non-structural-5A and -3 RAS at failure in the study confirms the EASL recommendation.....” Conclusions appropriately summarize the main findings that this study identified. 3. Third: Study limitations are enough well described; Future direction “suboptimal blood concentrations of DAA were measured in 2 patients among 7; these results could reflect different situations (drug interactions, suboptimal dosing errors, and suboptimal adherence) and warrant further investigation and wider-scale assessment of pharmacological data”.

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Name of journal: World Journal of Hepatology

Manuscript NO: 39428

Title: Factors associated with DAA virological treatment failure and resistance-associated substitutions description in HIV/HCV coinfecting patients

Reviewer’s code: 03764321

Reviewer’s country: Egypt

Science editor: Fang-Fang Ji

Date sent for review: 2018-06-15

Date reviewed: 2018-06-27

Review time: 12 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This is a very interesting study confirms the very low rate of treatment failure with all-oral DAA in HIV/HCV coinfecting patients, but a high risk of emergence of non-structural NS3 or NS5A RAS in patients with virological DAA failure. It also



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identified that low platelet count was associated with a higher probability of DAA failure. But there are from my point of view some comments and correction: 1. The title: it is better to write virological treatment failure in stead of virological failure and this should corrected in the whole manuscript. 2. In page 6 the words patients failing DAA replaced by with DAA treatment failure. 3. Key words: HIV, HCV, DAA, failure. To: HIV, HCV, DAA, treatment failure. 4. Page 8 introduction: has replaced by had. ; same page line 19: non virological treatment failure non should be removed virological treatment failure 5. Page 9: virological failure to virological treatment failure or just DAA treatment failure. 6. Page 10 : Data collection and definitions : You didn't mention what are the risk factors for both HIV & HCV infections 7. Page 10 : what do you mean by unkown at EOT? How it was unkown? 8. Page 13 : Factors associated with failure to Factors associated with treatment failure. 9. * You said we found that a low platelet count was significantly associated with a higher rate of virological treatment failure. Then you said that low platelet count is a surrogate marker of cirrhosis and then you said we failed to observe a significant relationship between cirrhosis and failure. Are the patients with low platelet count in your study had cirrhosis or the lowered number is due to something else? 10. InTable 1: Patients' characteristics at treatment initiation according to virological response Platelets < 100 Giga/L (n=408) 57 (14) 51 (13) 6 (43) 0.007 This calculations and others in your manuscript are not understandable what dose the in between () means is it percentage? if it is of what? In the attached file the manuscript with the suggested corrections. thank you and best wishes.

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