

25766 - Answering reviewers

**Comments to authors:**

Review for manuscript t# 25766 , **Treatment of chronic hepatitis C with direct-acting antivirals: the role of resistance**

We thank the reviewers for their kind and useful comments

Reviewers 1:

Jiménez-Perez et al carry out a well-structured, interesting and easy to read review about the role of HCV resistant variants to direct acting antivirals (DAA). I would only add a minor suggestion in the paragraph about host-dependent factors, where I would add some comments on the role of specific cytotoxic T cell restoration after DAA as a potential mechanism involved in complete HCV clearing (J Hepatol 2014; 61: 538-543, World J Gastroenterol 2015; 21(12): 3480-3491).

Further information about the role of specific cytotoxic T cell restoration after direct acting antivirals has been added to the manuscript in the section about Host-dependent factors (4.3)

Reviewers 2:

The article entitled "Treatment of chronic hepatitis C with direct acting antivirals: the role of resistance" Jimenez-Perez et al., is well written and well presented, however I have few concerns 1. Where the author describes the genome of virus, also describe the role of 5'UTR and 3'UTR. 2. What is the probability of occurrence of single site mutant and double site mutant? If we use single drug, what is the chances of occurrence of mutant against that drug and when we use combination of drugs acting on 2 different targets like polymerase and protease, what is the chances of occurrence of double site mutant? Already published, please include in your paper. 3. If you find papers, add the real life experience of Sofosbuvir + Daclatasvir and Sofosbuvir + Ledipasvir treatment failures / mutation rates. The paper is accepted for publication in World Journal of Gastroenterology after minor revision.

Relevant information concerning points 1 and 2 has been added to the manuscript. Concerning point 3, at the current time we are unable to find any published reports about treatment failures/mutation rates in real clinical practice using sofosbuvir plus daclatasvir or sofosbuvir plus ledipasvir. We have, though, added the suggestion at the end of the relevant section that evidence will appear shortly.

Reviewers 3:

The problem of resistance to DAA treatment of hepatitis C is very significant. Since DAA is such promising, but expensive way of HCV-infection treatment, it is very important to know the limitations that patients can face. This is an excellent paper that overviews the reasons for

resistance to DAA treatment. I have no problem with this manuscript, it is well and clearly written and provides the detailed information on possible negative outcomes of DAA treatment in HCV patients.

We thank the reviewer for the comment