6/15/2014

Dear Editor,

Thank you very much for the opportunity to further revise our manuscript (file name: 8162-review.doc). We have read the constructive and thorough criticism from the reviewers and have listed our responses to the suggestions below. We hope that you find our revision satisfactory.

Title: Hepatitis C virus in the HIV infected patient

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 8162

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer.
Review 1:
1. As suggested by reviewer 1 we provided an overview of the methodology used and changed the text accordingly:
We conducted a narrative review to provide an overview of HIV-HCV coinfection. A comprehensive computerized literature search was carried out in Pubmed and ClinicalTrials.gov to collect relevant articles. The review describes epidemiology, diagnose and the natural course of HCV as well as guidelines for HCV therapy in the context of HIV-HCV coinfection in the western world.

2. As suggested by review 1 we updated the text with the newest antiviral therapies and interactions in HIV-HCV coinfection and changed the text accordingly:
Therapy for HCV changes faster than international guidelines are updated and in the following section we will try to give an overview of current and future possible treatment strategies in HIV-HCV coinfected individuals. Pegylated (peg) IFN will still be the backbone of some HCV therapy combinations in 2014 and 2015, but is then expected to disappear from HCV therapy. We provide an overview of interferon free clinical trials including HIV infected individuals in table 1. Ribavirin (RBV) can be used to increase rates of sustained virological response (SVR) or to shorten treatment duration in pegIFN or IFN-free regimens and will probably remain in some HCV therapy strategies. Direct-acting antiviral (DAA) agents in HCV therapy target different steps of the viral lifecycle. DAAs comprise NS3/4A protease inhibitors, NS5B polymerase inhibitors, nucleoside/nucleotide analogues, non-nucleoside analogues inhibitors of the HCV RNA dependent RNA polymerase, cyclophilin inhibitors and antagonists of miRNA-122 (reviewed in (122)). Few of the DAAs are approved for HCV therapy (table 2) and the majority are in phase II or III development. The antiviral effect of one DAA can be optimized by combining several DAAs with or without RBV (table 3) and the combination strategy has shown that it is possible to gain sustained virological response with interferon-free regimens.

The first DAAs to be approved for HCV treatment was the NS3/4A protease inhibitor, telaprevir or boceprevir in combination with peg IFN and ribavirin. These compounds are on their way out of HCV therapy and are replaced with the nucleotide analogue, sofosbuvir in combination with RBV with or without peg IFN as the best treatment

option in HCV genotypes 1 and 4 infections. The addition of sofosbuvir to pegIFN/RBV (triple therapy) for 24 weeks increases SVR rates at week 12 after treatment termination (SVR12) to 76%. For genotype 2 infections the current best treatment option is the IFN-free regimen with sofosbuvir and RBV for 12 weeks with SVR12 rates of 88%. In genotype 3 infections the same regimen is approved and treatment duration is recommended to be extended to 24 weeks with SVR12 rates of 67%. Data regarding HCV genotype 5 and 6 is limited, however, sofosbuvir + pegIFN + RBV appears to be the best treatment option.

The next DAAs to be approved will most likely be simeprevir, faldaprevir and daclatasvir and available data from studies of HIV-HCV coinfected patients are summarized in table 2. However, treatment with DAAs is costly and the high costs will probably influence the choice of treatment strategy and result in first-, second- and third-line strategies in HCV treatment.

With the potent therapy strategies combining different DAAs with or without RBV, the SVR rates are not fundamentally different between HCV mono-infected and HCV-HIV coinfected patients. However, drug-drug interactions (DDI) with ART are of concern as most HIV infected individuals are treated for their HIV. Briefly, no clinically significant DDIs are reported between sofosbuvir and antiretrovirals. With respect to simeprevir, co-administration with antiretroviral inducers of CYP34A is not recommended and with respect to daclatasvir dose reduction is recommended when administered with specific antiretroviral drugs. Still, data are limited and more studies are warranted assessing DDIs with ART.

3. Additionally, we included a section on treatment of acute HCV infection

Review 2
1. We thank the reviewer for the very positive comments. In order to focus the contents on HIV-HCV coinfection we did not include facts about double or triple infections with hepatitis B virus.

Review 3
1. As suggested by reviewer 3 we added figure 1 and table 2 and 3 to make the manuscript more reader friendly.

Review 4
1. As suggested by the reviewer we revised the language by a mother tongue. Further, we updated the epidemiology section with iathrogen exposure and changed the text accordingly. References were reduces, however, guidelines from World Journal of Gastroenterology requires as least 100 references and we provide 131 references.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology.*

Sincerely yours,

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