Reviewer's comment (underlined) and answers

We would like to thank the reviewers for carefully reviewing our manuscript and providing us with valuable insights for the improvement of the text.

-Major points please make a schema/figura summarizing immune response against HCV virus (chapter 3)

A figure summarizing the immune responses against HCV infection was designed and added to chapter 3.

-Minor points Core tip and abstract: please change the last sentences of both, which are now very general, giving more details on the content of the review.

To make the Core tip and the Abstract more specific, we mentioned that the article reviews progress in the development of a preventive and therapeutic vaccine against the hepatitis C virus in the context of Peptide vaccines, Recombinant protein vaccines, HCV-like particle, DNA vaccines and Viral vectors expressing HCV genes."

-Chapter 1: Please give direct example of direct acting antivirals and mention explicitly type and incidence of adverse effects.

The direct acting antivirals include fever, fatigue, chills and depression. Such adverse effects may occur in more than 5% of those who use the treatment.

-Chapter 2: the sentence "P7 is the first non-structural (NS) protein located after structural proteins with unknown function"; Located in the virus genome? Please explain, the sentence is not very clear.

Considering the HCV genome, P7 gene encodes the first non-structural (NS) protein and is located after the genes which encode structural proteins. This has been corrected in the manuscript. We also gave further information that it forms the ion channels that seem to be essential for HCV efficient assembly, release and production.

-Chapter 3.2: the sentence "Recent studies suggest that patients with HCV infection show an elevated level of activated B cells and people with defects in antibodies experience rapid progression of disease, emphasizing the role of humoral immunity in HCV [60-62]. Patients with hypogammaglobulinaemia could spontaneously resolve acute hepatitis C, suggesting that humoral immunity is essential for HCV clearance [63]." seems contadictory, please give more details.

Your comments was true and we corrected it. Now, there should not be any contradictory statement observed.

-Chapter 3.3: even the sentence "Patients who lack efficient cytotoxic T cell response develop persistent hepatitis C infection but the magnitude of cytotoxic T cell response is associated with the clinical outcome [74]" seems contradictory, please explain.

Your comments was true and we corrected it. Now, there should not be any contradictory statement observed.

-Chapter 4.1: Was really just one individual reported in the literature as presenting an infection from a quasispecies of HCV? This does not sounds like a very high contribution of quasispecies to HCV infections globally. Please revise and/or provide more detailes.

HCV quasispecies are kind of hepatitis C viruses with high rate of genetic variations. We do not have information how it is important globally but our main aim was to mention that this phenomenon can occur for HCV no matter how insignificant it may be in the global perspective.

-Chapter 4.2: please check the word "persistent" in the title The sentence "In exhaustion, T cells lose their ability to produce IL-2 which is essential for T cell production" is not clear, please revise.

The word “persistent” was changed to “persistence”. We provided more information regarding T-cell exhaustion: In T cell exhaustion, T cells are in a state of dysfunction. This phenomenon can develop during many chronic infections like HCV. These cells lose their ability to produce IL-2 which is essential for the production of T cells and show sustained expression of inhibitory receptors.

-Chapter 4.3, first paragraph: Is it true that no other mammal could besides human, chimpanzees and tree shrews can be infected with HCV virus? Not even other primate? Why is this? Please give more details on proofs of this and insight on cellular/molecular reasons.

Other than humans, chimpanzees[128] and a non-rodent small mammal named Tupaiabelangeri[129], also known as the tree shrew, are naturally susceptible to HCV infection.

Other organisms, even if a few of them are susceptible to HCV infection, are not normally considered for studies due to ethical reasons and the high expenses associated with keeping and taking care of them. In addition, they show high rates of genetic mutations which makes them not suitable model organisms for studies of HCV infection.

-Chapter 4.3, last paragraph: Is the genome of JFH1 the same as HCV? What is the difference between the two viruses? Please give more details

More information was added: The first successful tissue model of HCV infection was developed in 2005 using the HCV/JFH1 cell culture system [140]. Whole genome of The JFH1 virus was separated from a Japanese patient with fulminant hepatitis, it was then multiplied with PCR, cloned and was named JFH1. The JFH1 virus is one of the 2a genotype, has a full-length HCV genome. This culturing system efficiently maintains the replication of hepatitis C virus in human hepatoma cell line Huh7 and produces fair titers of cell-cultured derived HCV particles (HCVcc) with natural infectious properties.

-Chapter 5, first sentence: please revise "following complications".

Following complications was changed to “the development of clinical complications”.

-Chapter 5.3: Please give a more organized introduction explaining in general terms how DNA vaccines work.

The mechanism of action was added. DNA vaccine includes the nucleotides encoding an antigenic portion of the virus such as the viral core region or envelope region. The DNA vaccine is taken up in to the host cell, translated and the protein is produced. These proteins are processed via the endogenous MHC class 1 pathway and promoted Cell-mediated immune responses (CMI).

-Chapter 5.4, first paragraph: The sentence “since there is no HLA restriction” is not clear, please give more details on why “Compared to DNA vaccines, vector based vaccines introduce a broader range of viral epitopes and induce broader CD4+ and CD8+ T cell responses” Conclusion is too long and not clear: please revise.

Vector-based vaccines express vast and diverse epitopes that would result in the activation of an extended types of immune cells. Conclusion was revised and shortened.

-This review is well-written. The authors should add the descriptions regarding recent anti-HCV therapies, such as DAA, in the Abstract.

The following paragraph was added about recent anti-HCV therapies in the Abstract: Recent anti-HCV therapies are interferon-free direct-acting antiviral (DAA) regimens for HCV such as Simeprevir, Sofosbuvir and Ledipasvir which have effects on non-structural (NS) proteins. DAA regimens have several advantages such as specifically targeting HCV viral replication, accompanied by very high SVR rates and lower side effects such as flu-like syndrome.