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Madrid, May 12th, 2017

Dear Editor:

Thank you for the comments following the review of the paper entitled **"TENOFOVIR VERSUS LAMIVUDINE PLUS ADEFOVIR IN CHRONIC HEPATITIS B: TENOSIMP-B STUDY."** We have tried to include all the suggestions in this latest version and have listed a point-by-point response to the reviewer' comments below. In addition, we have fully revised the manuscript and updated appropriate sections in the manuscript that have been changed with the track changes tool. We hope that you will find this revised manuscript suitable for publication in your journal.

We hope that the answers provided to the comments would be enough satisfactory to consider the submission of our work. Thank you in advance for your interest.

Yours sincerely,

Miguel Angel Casado on behalf authors.

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Comments to the Author.

For a better comprehension of the article, minor changes in wording (highlight in yellow) have been made. For example: in the abstract section, the phrase: "*in the maintenance of virologic response in patients with chronic hepatitis B (CHB) with prior failure with LAM***"** has been changed to: "*in the maintenance of virologic response in patients with chronic hepatitis B (CHB) and prior failure with LAM*".

REVIEWER: 1

This study focused on the efficacy and safety of Tenofovir disoproxil fumarate versus Lamivudine + adefovir in patients with chronic hepatitis B with prior failure with Lamivudine. Several points require further attention:

1. In clinical practice, obese people often accompanied with diabetes or hypertension which would lead to deterioration in renal function. Whether these patients included or not in the study population?

We did not restrict the inclusion of obese people or patients with diabetes or hypertension in the study. This information has been added in table 1. There are not significant differences between both groups of therapies regarding these comorbidities.

Characteristic	**TDF (N = 22)**	**LAM+ADV (N = 24)**	**TOTAL (N = 46)**	**p-value**
Patients with and without diabetes mellitus or hypertension - number (%)				0.247
With	2 (9.1)	6 (25.0)	8 (17.4)	
Without	20 (90.9)	18 (75.0)	38 (82.6)	

2. The patients with HBV-related cirrhosis or compensated fibrosis should be described in the study population, and the efficacy and safety of TDF and LAM+ADV should be analyzed among these patients.

Only four patients had liver cirrhosis and the proportion of cirrhosis was not different between both groups of therapy. This information has been added in table 1.

Characteristic	TDF (N = 22)	LAM+ADV (N = 24)	TOTAL (N = 46)	p-value
Fibrosis (F) state - number (%)				0.336
<F4	19 (86.4)	23 (95.8)	42 (91.3)	
F4	3 (13.6)	1 (4.2)	4 (8.7)	

REVIEWER: 2

Design of the study is excellent, and study was well made. Duration of the phase IV study was 48 weeks. Sustained virologic suppression was 100% in both treated groups. All patients in both groups maintained HBeAg negativity during study period. None of the patients lost HBs antigen. Not only virologic response, but also adverse effects were comparable between tenofovir vs. lamivudine + adefovir study group. Adherence was slightly lower in lamivudine + adefovir study group, but not significantly. The total average hospital expense per patient was significantly lower in tenofovir group. Paper needs only minimal changes:

1. Abstract should be given at the begining of an article.

The suggested modification has been applied.

2. Please add viral load and HBe/antiHBe status in the patient with prematurely stopped treatment (tenofovir) due to adverse reactions.

This patient was included in the study and started treatment with tenofovir on October 20, 2011. Adverse reactions began on October 23, 2011 and for this reason, he stopped tenofovir treatment on November 3, 2011. This information has been added in the manuscript (Results – Safety).

For this patient, we only have baseline information. All patients, including this patient who prematurely stopped tenofovir treatment, had undetectable viral load, HBsAg + and HBeAg - (inclusion criteria) at the beginning of the study. Besides, this patient was anti-HBe +.

REVIEWER: 3

According to recently research, TDF have been proved which can effectively rescue HBV drug resistance, and this research need to enroll more patients to demonstrate the difference between two groups. From economical point, given entecavir would be an option to save cost.

The alternative with entecavir is not the best one for saving costs. Patients included in the study had a prior failure to lamivudine. In these cases, patients would need a dose of entecavir of 1 mg per day, and consequently treatment costs would increase significantly.

List all patients' viral load at start of rescuing and monitor anti-virus responding.

All patients had an undetectable viral load, HBsAg + and HBeAg – (inclusion criteria) and did not change during the study.