OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

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Hepatitis Monthly
Article DOI: 10.5812/hepatmon.118721
Published in: Hepatitis Monthly: 21(10); e118721

Peer Review Report for "Comparison of Tenofovir Alafenamide and Entecavir Therapy in Patients with Chronic Hepatitis B Initially Treated with Tenofovir Disoproxil: A Retrospective Observational Survey"

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Review Timeline:

Submit Date:	16 Aug 2021
Revised Date:	26 Dec 2021
Accepted Date:	28 Dec 2021

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0) 6 Sep 2021

Dear AE,

I reviewed the manuscript entitled “Comparison of Tenofovir Alafenamide and Entecavir Therapy in Patients with Chronic Hepatitis B Initially Treated with Tenofovir Disoproxil”. The topic is not novel, but the design of the study is good, and the findings have potentials to contribute to the literature. Please see my comments below which are mainly related to the writing styles and data presentation. I have also suggested consultation with an experienced statistician to revise sample size and power calculation.

1- The manuscript needs an English editing. There are several errors in grammar, sentence structure, and punctuation in the manuscript which sometimes make it difficult to follow the

paper properly.

2- Abstract: “The treatment of patients with chronic hepatitis B with tenofovir disoproxil fumarate (TDF) should be changed to the use of tenofovir alafenamide fumarate (TAF) or entecavir (ETV) …”. I would suggest the authors to tone down this statement given that it is only correct for patients with or exposed to the risk of bone or renal-related side effects. The statement by the authors in the Background section (page 2) is accurate, but in the abstract, it needs to be mitigated.

3- Abstract: LDLC should be spelled out.

4- Methods (page 2): “The Centers in the Eastern and South-Eastern Anatolia regions of Turkey with intermediate endemicity of CHB were included”. The authors are suggested to provide more details regarding the level and type of clinical services provided in these services. For example, it would be informative to know if they were primary care clinics, specialist hepatology clinics, infectious diseases clinics, hospital-based clinics, etc.

5- Methods (page 3): “ETV group was consisted of 107 patients who switched to ETV, TDF group was 237 patients who switched to TAF”. I was wondering if TDF has been used correctly in this sentence. My understanding is that the second group was supposed to be called “TAF”. In the next sentence, the authors stated, “It was used to treat patients with ETV or TAF at the discretion of the treating physician” which was not clear to me as well.

6- Statistics (page 3): The sample size calculation is not clear. The authors stated, “treatment response rates of 94% and 86% were determined for TAF and ETV, respectively”, which means that they calculated the sample size for comparison of treatment response (I assume it means HBV DNA suppression) between TAF and ETV. However, the objective of the study is “to compare the changes in treatment efficacy … of transition from TDF to ETV or TAF”. In fact, the authors aimed to conduct two comparisons, independently for: 1) treatment efficacy before and after ETV; 2) treatment efficacy before and after TAF. Then it means that the authors need to calculate the sample size for each of these two comparisons separately and based on the principles of before-after comparisons. I would suggest the authors to consult with an experienced statistician to revise their sample size and power calculation.

7- Figure 1: Please add label for Y axis.

8- Table 1: Some p values were reported as >0.05. Please replace them with actual values and for each comparison separately. Please also describe hip T score and spine T score in footnote.

9- Results (page 4): “The HBV-DNA of 196 patients were evaluated both at onset and the sixth month”. It means that only about 55% of participants were tested for HBV DNA which looks low. I was wondering if the authors can make comments about it.

10- Results: “Rate” in epidemiology is a time-dependent measure (e.g., incidence rate which refers to the new cases of a diseases during a specific time). The authors have used “rate” incorrectly throughout the manuscript. For example, in page 4, they stated, “this increase in undetectable HBV-DNA rates in the sixth month …”, which is not correct and should be changed to “proportion of undetectable HBV-DNA”. The authors need to review the manuscript carefully and change “rate” to a correct term based on the definition it is used for.

11- Results (page 5): “Creatinine levels increased significantly in the 6th month compared to the baseline levels among patients who switched to TAF”. It is not consistent with Figure 3 which shows a decrease in Cr levels. Please also check the rest of the results section to

make sure about consistency of the text with the figures.
12- Figures 3 and 4: It is not clear what * and ** mean.
13- Limitations of the study should be also discussed in the Discussion section.

REFEREE: Reviewer | **Revision** (0) 14 Sep 2021

Dear editor,

ABSTRACT:
1- There is no evidence for first sentence: "The treatment of patients with chronic hepatitis B with tenofovir disoproxil fumarate (TDF) should be changed to …..
2- There is significant dissociation between results and conclusion
Patients and Methods:
1- Determination of GFR in chronic hepatitis and cirrhosis by routine is unreliable. what is your method for GFR measurement?
Results:
1- BMD is not a diagnosis…"two most common causes were found as BMD and osteoporosis…."
Discussion:
1- There are many controversy about creatinine : " Creatinine levels increased significantly in the 6th month compared to the baseline levels among patients who switched to TAF…" AND "The estimated glomerular filtration rate increased significantly in the 6th month compared to the baseline rate in patients who switched from TDF to TAF …) AND "There was no difference between the two treatment groups in terms of the change in creatinine values"

REFEREE: Reviewer | **Revision** (0) 18 Sep 2021

Dear Editor,

General summary
Hepatitis B virus (HBV) infection is a global heath problem. Current nucleotide or nucleoside analog treatments such as TDF, TAF, and ETV can efficiently control viremia. The side effects of these treatment mainly include renal toxicity, reduction of bone density, etc. It is critical to identify the most effective treatments for patients that result in minimal side effects. In this manuscript, the authors examined patients, who had been under TDF treatment previously and have switched to either ETV or TAF treatment due to various side effects elicited by TDF. The authors compared serum DNA levels, ALT, AST, kidney function, bone density, lipid panel before and after treatment switch, and reported significant improvement of kidney function and increase of LDL cholesterol 6 months after the switch.

The findings are interesting, and the data presented are explained in a clear manner. However, I have some concerns that need to be further addressed.

Comments:
1. A small cohort of the patient has cirrhosis or HDV infection. It would be great if additional analyses (similar to Figure 2-4) could be conducted for these patients specifically to see if

switch of treatment could be beneficial to these patients with more severe liver diseases.

2. The HBeAg status of these patients are not indicated in this manuscript, it would be better to also include this status and conduct additional analyses to see if it affect the outcome of the treatments.

3. Page 7, middle section, ‘On the other hand, in the 6th month, creatinine levels increased significantly among patients who switched to TAF, whereas no significant difference was determined in those who switched to ETV.’ It is suppose to be ‘decreased’, please check.

4. Same paragraph, ‘This study indicated that the treatment changes were safety for TAF and ETV drugs in terms of renal functions’, should be ‘safe’.

REFEREE: Associate Editor | **Revision** (0) 26 Sep 2021

Dear Editor
The manuscript entitled "Comparison of tenofovir alafenamide and entecavir therapy in patients with chronic hepatitis B initially treated with tenofovir disoproxil" was reviewed by peer-review team. The results can be of interest but there are major concerns raised by the reviewers (The authors shouldn’t forget to download an attached file for seeing the one reviewer’s comments). I want to add more minor and major comments as following:
1. To let readers know this survey is not a clinical trial, I strongly suggest that the title be ended with the following phrase: “A Retrospective Observational Survey”.
2. Please clarify type of data collected at t = 0 and t = 6 months of treatment in the Methods of ABSTRACT. You can also remove the names of statistical tests in this part.
3. Some general words such as ‘vital signs’ and ‘biomarkers’ in the Results part of ABSTRACT should be more explained.
4. This sentence of Methods needs to be revised: “A total of 344 patients who received TDF at these centers with the inclusion criteria and were included in the study and TDF treatment was discontinued.”
5. Viral load should be expressed as IU/ml. Please correct it in the Methods (page 3).
6. Inclusion criteria listed in page 2 were duplicated in paragraph 3 of page 3. Please remove one of them.
7. Considering confidence level of 95%, power of 80%, p1 = 0.94% and p2 = 0.94%, the number of 220 samples in each study group would be needed. Could you tell us which formula you used to calculate sample size?
8. The sample size seems to be relatively enough. What about parametric test? Were all data non-normally distributed?
9. The Result section is so long! You can ignore the text where the related data is given in the Figures 1 to 4.
10. In Table 1, there are multiple variables in one row (Cirrhosis/HT/DM or Anti-HCV/ HIV/ Delta antibody). Please write each variable in single row.
11. P-values quantified in the text (page 5) for ALT normalization in the ETV and TAF groups are different from ones indicated in Figure 2!
12. The amount of changes in kidney and bone variables or lipid profiles are different in the text (page 5) from Figures 3 and 4!

13. Please give the volume number and pages for ref. 23.
14. Link in ref. 30 doesn't work. Please fix it.
15. The references 32 and 33 are duplicate.
16. What does (**) mean in Figure 2 legend.
17. Could you merge the upper and lower bars in the Figure 2? It would make it more simple and clear.

Regards,

Seyed Moayed Alavian: EIC | **Revision** (0) 26 Sep 2021

Dear Authors,

Thank you for your submission. Please follow the peer-review comments and submit a revision.

Regards,
EIC

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Reviewers' Comments:

Reviewer 1:

General summary

Hepatitis B virus (HBV) infection is a global health problem. Current nucleotide or nucleoside analog treatments such as TDF, TAF, and ETV can efficiently control viremia. The side effects of these treatments mainly include renal toxicity, reduction of bone density, etc. It is critical to identify the most effective treatments for patients that result in minimal side effects. In this manuscript, the authors examined patients, who had been under TDF treatment previously and have switched to either ETV or TAF treatment due to various side effects elicited by TDF. The authors compared serum DNA levels, ALT, AST, kidney function, bone density, lipid panel before and after treatment switch, and reported significant improvement of kidney function and increase of LDL cholesterol 6 months after the switch.

The findings are interesting, and the data presented are explained in a clear manner. However, I have some concerns that need to be further addressed.

Comments:

1. A small cohort of the patient has cirrhosis or HDV infection. It would be great if additional analyses (similar to Figure 2-4) could be conducted for these patients specifically to see if switch of treatment could be beneficial to these patients with more severe liver diseases.

In subgroup analyzes:

For patients with cirrhosis, according to the baseline in the sixth month of treatment, the rate of undetected HBV-DNA increased from 77.8% to 83.3% in the ETV group and increased from 91.7% to 100% in the TAF group. The patients who have Delta co-infection, according to the baseline in the sixth month of treatment had no difference in undetectable HBV-DNA rates both in ETV and TAF group, 83.3% vs 93.5% respectively.

2. The HBeAg status of these patients are not indicated in this manuscript, it would be better to also include this status and conduct additional analyses to see if it affect the outcome of the treatments.

HBeAg positivity was detected in 79 (22.4%) patients. HBV-DNA was evaluated in 31 patients in the TAF group and 19 patients in the ETV group, both at baseline and at the sixth

month. In these TDF-experienced patients, only 1 patient in the TAF group and 2 patients in the ETV group had detectable HBV-DNA at baseline, and HBV-DNA was detectable at 6 months in these patients.

3. Page 7, middle section, ‘On the other hand, in the 6th month, creatinine levels increased significantly among patients who switched to TAF, whereas no significant difference was determined in those who switched to ETV.’ It is suppose to be ‘decreased’, please check.

Fixed to 'Decreased'.

4. Same paragraph, 'This study indicated that the treatment changes were safety for TAF and ETV drugs in terms of renal functions', should be 'safe'.

Fixe to ‘safe’

Reviewer 2:

I reviewed the manuscript entitled "Comparison of Tenofovir Alafenamide and Entecavir Therapy in Patients with Chronic Hepatitis B Initially Treated with Tenofovir Disoproxil". The topic is not novel, but the design of the study is good, and the findings have potentials to contribute to the literature. Please see my comments below which are mainly related to the writing styles and data presentation. I have also suggested consultation with an experienced statistician to revise sample size and power calculation.

1- The manuscript needs an English editing. There are several errors in grammar, sentence structure, and punctuation in the manuscript which sometimes make it difficult to follow the paper properly.

Edited in English.

2- Abstract: "The treatment of patients with chronic hepatitis B with tenofovir disoproxil fumarate (TDF) should be changed to the use of tenofovir alafenamide fumarate (TAF) or entecavir (ETV) …". I would suggest the authors to tone down this statement given that it is only correct for patients with or exposed to the risk of bone or renal-related side effects. The statement by the authors in the Background section (page 2) is accurate, but in the abstract, it needs to be mitigated.

Changed to. 'In chronic hepatitis B patients with osteoporosis or renal dysfunction, switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide fumarate (TAF) or entecavir (ETV) may be the right choice.'

3- Abstract: LDLC should be spelled out.

Changed to. 'low-density lipoproteins cholesterol'

4- Methods (page 2): "The Centers in the Eastern and South-Eastern Anatolia regions of Turkey with intermediate endemicity of CHB were included". The authors are suggested to provide more details regarding the level and type of clinical services provided in these services. For example, it would be informative to know if they were primary care clinics, specialist hepatology clinics, infectious diseases clinics, hospital-based clinics, etc.

Changed to; 'It was conducted in tertiary care centers, infectious diseases and gastroenterology clinics in Eastern and Southeastern Anatolia regions of Turkey, where CHB is moderately endemic.'

5- Methods (page 3): "ETV group was consisted of 107 patients who switched to ETV, TDF group was 237 patients who switched to TAF". I was wondering if TDF has been used correctly in this sentence. My understanding is that the second group was supposed to be called "TAF". In the next sentence, the authors stated, "It was used to treat patients with ETV or TAF at the discretion of the treating physician" which was not clear to me as well.

Changed to; 'A total of 344 patients who received TDF at these centers with the inclusion criteria and were included in the study and TDF treatment was discontinued. These patients were divided into two groups including ETV group and TAF group. ETV group was consisted of 107 patients who switched to ETV, TAF group was 237 patients who switched to TAF. It was used to treat patients with ETV or TAF at the discretion of the treating physician.'

6- Statistics (page 3): The sample size calculation is not clear. The authors stated, "treatment response rates of 94% and 86% were determined for TAF and ETV, respectively", which means that they calculated the sample size for comparison of treatment response (I assume it means HBV DNA suppression) between TAF and ETV. However, the objective of the study is "to compare the changes in treatment efficacy … of transition from TDF to ETV or TAF". In

fact, the authors aimed to conduct two comparisons, independently for: 1) treatment efficacy before and after ETV; 2) treatment efficacy before and after TAF. Then it means that the authors need to calculate the sample size for each of these two comparisons separately and based on the principles of before-after comparisons. I would suggest the authors to consult with an experienced statistician to revise their sample size and power calculation.

Instead of the sampling calculation made on the undetected HBV-DNA, the sample calculation was made for the eGFR from other variables that were compared according to your request. This calculation is carried out by the biostatistics expert involved in our study.

The sampling calculation was made on the assumption that the change from TDF to TAF or ETV would have an indifferent effect on renal functions. Using the GFR values after at least 6 months of follow-up from the literature, it was taken as 80% power, 95% confidence level and margin of 5 units. The minimum number of samples required in each group was calculated as 102.

7- Figure 1: Please add label for Y axis.

We added a label for Y-axis.

8- Table 1: Some p values were reported as >0.05. Please replace them with actual values and for each comparison separately. Please also describe hip T score and spine T score in footnote.

The actual values of p are given separately.

Added to; ‘Bone mineral density in the lumbar spine and a region of the hip close to the hip joint was calculated using dual energy x-ray absorptiometry (DEXA).’

9- Results (page 4): “The HBV-DNA of 196 patients were evaluated both at onset and the sixth month”. It means that only about 55% of participants were tested for HBV DNA which looks low. I was wondering if the authors can make comments about it.

This study is a retrospective real-life study. It was because the following physicians did not perform HBV-DNA examination, preferably at the 6th month. This limitation has been added to the limitation section.

10- Results: "Rate" in epidemiology is a time-dependent measure (e.g., incidence rate which refers to the new cases of a diseases during a specific time). The authors have used "rate" incorrectly throughout the manuscript. For example, in page 4, they stated, "this increase in undetectable HBV-DNA rates in the sixth month …", which is not correct and should be

changed to "proportion of undetectable HBV-DNA". The authors need to review the manuscript carefully and change "rate" to a correct term based on the definition it is used for.

We changed the term to; 'proportion of undetectable HBV-DNA'

11- Results (page 5): "Creatinine levels increased significantly in the 6th month compared to the baseline levels among patients who switched to TAF". It is not consistent with Figure 3 which shows a decrease in Cr levels. Please also check the rest of the results section to make sure about consistency of the text with the figures.

We fixed the word to 'Decreased'.

12- Figures 3 and 4: It is not clear what * and ** mean.

Added to, 'Figure 3. * Comparison of changes in markers in the first six months between treatment groups; Mann-Whitney U test, ** Comparison of the values of the markers at baseline and the sixth month in the treatment arm, Wilcoxon Signed-Ranks Test)

Figure 4. * Comparison of changes in markers in the first six months between treatment groups; Mann-Whitney U test, ** Comparison of the values of the markers at baseline and the sixth month in the treatment arm, Wilcoxon Signed-Ranks Test'

13- Limitations of the study should be also discussed in the Discussion section.

The main strengths of this study are that real-life data were presented in a multicenter study from a region where hepatitis B infection is moderately endemic. To the best of our knowledge, our study is the largest series comparing treatment responses and changes in parameters with these treatment regimens. However, the use of retrospective analysis is one of the limitations of this study, and our results must be confirmed by prospective studies with larger series. Another limitation is that in this retrospective study, all parameters evaluated in the study were not demanded, with the preference of the treating physician. This resulted in a reduction in the number of patients to evaluate each effect.

Reviewer 3:

ABSTRACT:

1- There is no evidence for first sentence: "The treatment of patients with chronic hepatitis B with tenofovir disoproxil fumarate (TDF) should be changed to …..

As stated in the EASL 2017 guideline, this sentence has been changed within the recommendation to switch from TDF to TAF or ETV in bone diseases and renal changes.

‘Treatment of patients with chronic hepatitis B with tenofovir disoproxil fumarate (TDF) may be the right choice for those with bone and kidney side effects or risk exposure to switch to tenofovir alafenamide fumarate (TAF) or entecavir (ETV)’

2- There is significant dissociation between results and conclusion ‘

Please re-evaluate after the changes we have made

Patients and Methods:

1- Determination of GFR in chronic hepatitis and cirrhosis by routine is unreliable. what is your method for GFR measurement?

Added to the method section. ‘Renal function was assessed with serum creatinine, estimated glomerular filtration rate(eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) Study equation, and serum phosphate.’

Results:

1- BMD is not a diagnosis…" two most common causes were found as BMD and osteoporosis…."

Change to, ‘two most common causes were found as use of drugs affecting BMD and osteoporosis.’

Discussion:

1- There are many controversy about creatinine : " Creatinine levels increased significantly in the 6th month compared to the baseline levels among patients who switched to TAF…" AND "The estimated glomerular filtration rate increased significantly in the 6th month compared to the baseline rate in patients who switched from TDF to TAF …) AND "There was no difference between the two treatment groups in terms of the change in creatinine values"

Fixed to 'Decreased'.

Result; Creatinine levels decreased significantly in the 6th month compared to the baseline levels among patients who switched to TAF, whereas no significant difference was determined in those who switched to ETV (p=0.011 and p=0.213, respectively).

Discussion; On the other hand, in the 6th month, creatinine levels decreased significantly among patients who switched to TAF, whereas no significant difference was determined in those who switched to ETV.

Associate Editor's Comments:

Associate Editor 1:

Dear Editor

The manuscript entitled "Comparison of tenofovir alafenamide and entecavir therapy in patients with chronic hepatitis B initially treated with tenofovir disoproxil" was reviewed by peer-review team. The results can be of interest but there are major concerns raised by the reviewers (The authors shouldn't forget to download an attached file for seeing the one reviewer's comments). I want to add more minor and major comments as following:

1. To let readers know this survey is not a clinical trial, I strongly suggest that the title be ended with the following phrase: "A Retrospective Observational Survey".

added to ‘A Retrospective Observational Survey’ end of the title

2. Please clarify type of data collected at t = 0 and t = 6 months of treatment in the Methods of ABSTRACT. You can also remove the names of statistical tests in this part.

The virological response was assessed with undetected HBV DNA. Serum alanine amino acid transferase (ALT) values were used to evaluate the biochemical response. For renal functions, serum creatinine, phosphate, and glomerular filtration rate results were recorded. Bone health, spine and hip T score, and finally lipid profile, serum total cholesterol, low- and high-density lipoprotein, and triglyceride levels were evaluated.

3. Some general words such as ‘vital signs’ and ‘biomarkers’ in the Results part of ABSTRACT should be more explained.

Biomarkers such as platelet count, ALT, phosphorus, creatinine, total bilirubin, albumin, lipid profiles,

4. This sentence of Methods needs to be revised: “A total of 344 patients who received TDF at these centers with the inclusion criteria and were included in the study and TDF treatment was discontinued.”

A total of 344 patients who were changed to TAF or ETV by discontinuing TDF according to the inclusion criteria in these centers were included in the study.

5. Viral load should be expressed as IU/ml. Please correct it in the Methods (page 3).

We edited this part as 'IU/ml'

6. Inclusion criteria listed in page 2 were duplicated in paragraph 3 of page 3. Please remove one of them.

We removed one of the duplicated words.

7. Considering confidence level of 95%, power of 80%, p1 = 0.94% and p2 = 0.94%, the number of 220 samples in each study group would be needed. Could you tell us which formula you used to calculate sample size?

http://powerandsamplesize.com/Calculators/Compare-2-Means/2-Sample-Non-Inferiority-or-Superiority

This calculator uses the following formulas to compute sample size and power, respectively:

$$n_A = \kappa n_B \text{ and } n_B = \left(1 + \frac{1}{\kappa}\right)\left(\sigma \frac{z_{1-\alpha} + z_{1-\beta}}{\mu_A - \mu_B - \delta}\right)^2$$

$$1 - \beta = \Phi\left(z - z_{1-\alpha}\right) + \Phi\left(-z - z_{1-\alpha}\right) \quad , \quad z = \frac{\mu_A - \mu_B - \delta}{\sigma\sqrt{\frac{1}{n_A} + \frac{1}{n_B}}}$$

where

$\kappa = n_A / n_B$ is the matching ratio
σ is standard deviation
Φ is the standard Normal distribution function
Φ^{-1} is the standard Normal quantile function
α is Type I error
β is Type II error, meaning $1 - \beta$ is power
δ is the testing margin

8. The sample size seems to be relatively enough. What about parametric test? Were all data non-normally distributed?

Although the sample was large, non-parametric tests were used in the statistical analysis since it was noticed that the data evaluated for comparison did not fit the normal distribution.

9. The Result section is so long! You can ignore the text where the related data is given in the Figures 1 to 4.

We removed specified points .

10. In Table 1, there are multiple variables in one row (Cirrhosis/HT/DM or Anti-HCV/ HIV/ Delta antibody). Please write each variable in single row.

The table is arranged like this.

11. P-values quantified in the text (page 5) for ALT normalization in the ETV and TAF groups are different from ones indicated in Figure 2!

We corrected this part.

12. The amount of changes in kidney and bone variables or lipid profiles are different in the text (page 5) from Figures 3 and 4!

In the text, the variables of renal-bone and lipid profile, baseline and 6th month values were subtracted from each other and the change was calculated and the median (IQR) of this change was presented. Likewise, baseline and sixth month data were presented as median (IQR) in Figures 3 and 4. However, it was thought that it was not understood that it was presented in this way. Therefore, graphs are presented as line graphs and mean±SD, and the mean of change from baseline to month six is presented in text.

13. Please give the volume number and pages for ref. 23.

References have been rearranged.

14. Link in ref. 30 doesn't work. Please fix it.

We fixed the link.

15. The references 32 and 33 are duplicate.

References have been rearranged.

16. What does (**) mean in Figure 2 legend.

presented in figure 2. '* Comparison of the values of markers at baseline and the sixth month in the treatment arm, McNemar Test'

17. Could you merge the upper and lower bars in the Figure 2? It would make it more simple and clear.

Upper and lower bars are combined.

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (1) 19 Dec 2021

Dear EIC,

1- In Abstract, please give the important findings about changing of HBV DNA, renal function tests and bone markers among two studied groups.
2- There is significant dissociation between results and conclusion of Abstract. Please revise the Conclusion part of Abstract section.
3- Could you clarify the first paragraph of Patients and Methods part (page 2)? Were all 17 invited centers tertiary care centers? Were infectious diseases and gastroenterology clinics located in tertiary care centers? Were they independent or hospital-based clinic? How about 10 responder centers?
4- The Result section is so long! It is better to ignore the text where the data was given in the figures 1 to 4.
5- For subgroup analyzes (page 5, lines 182-186), could you please give the related p-values?
6- Figure 1: Please add values for Y axis.
7- I edited the manuscript for minor writing errors. Please see the attached file.

Thanks

Seyed Moayed Alavian: EIC | **Revision** (1) 20 Dec 2021

Dear Authors,

Thank you for submitting the revised manuscript. Associate editor has asked for additional corrections, including the English edits, before considering your manuscript for publication.

Regards,
EIC

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Associate Editor 1:

1- In Abstract, please give the important findings about changing of HBV DNA, renal function tests and bone markers among two studied groups.

Added

2- There is significant dissociation between results and conclusion of Abstract. Please revise the Conclusion part of Abstract section.

Revised

3- Could you clarify the first paragraph of Patients and Methods part (page 2)? Were all 17 invited centers tertiary care centers? Were infectious diseases and gastroenterology clinics located in tertiary care centers? Were they independent or hospital-based clinic? How about 10 responder centers?

Appropriate changes have been made.

4- The Result section is so long! It is better to ignore the text where the data was given in the figures 1 to 4.

The data thought to be in the figures were removed.

5- For subgroup analyzes (page 5, lines 182-186), could you please give the related p-values?

Added

6- Figure 1: Please add values for Y axis.

We added a label for Y-axis.

7. I edited the manuscript for minor writing errors. Please see the attached file.

OPEN PEER REVIEW

Revision (2)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (2) 28 Dec 2021

Dear EIC,

All reviewers' comments and recommendations were addressed by the authors and this manuscript can now be considered for publication in our journal. In addition, I edited the manuscript for minor writing errors. Please see the attached file.

Regards

Seyed Moayed Alavian: EIC | **Revision** (2) 28 Dec 2021

Dear Authors,

I am delighted to inform that your manuscript is accepted for publication.

Regards,
EIC