Changzhou, September 4th, 2018

Dear Editors,

We appreciate greatly the Editors and Reviewers for their helpful comments and suggestions for improving this manuscript. We have addressed the comments and suggestions and making manuscript text modifications that are presented in a resubmitted manuscript. The changes in the resubmitted manuscript text are in blue. Point-by-point responses are included below and shown as blue text for ease of review.

Point-by-point response to Reviewers

Reviewer 1

Lu et al. present a case study illustrating that the risk of HCC is not negligible during treatment with TAF (as is the case with other potent NAs TDF and ETV). This case also demonstrates the complexity of treating HBV-infected patients with several previous lines of anti-HBV treatment, multi-drug resistance, and residual HBV DNA replication during TDF (with no evidence of TDF resistant mutant variants). The case is for the most part clear, however, there are certain issues that need to be addressed. HCC developed within a span of 5 months after TAF initiation. It could very well be that HCC had already started developing prior to TAF initiation and HBV suppression due to TAF would not really matter. This needs to be explained in the discussion.

Thank you for the critical comment. It is true that successful antiviral therapy is beneficial in preventing cirrhosis progression and HCC development. The pathogenesis of HCC is thought to be multifactorial, and liver cirrhosis is an important risk factor for HCC. Even though a potent NA which can maintain HBV suppression, reduces but does not eliminate the risk of HCC development [reference #1]. These have been added in the discussion section (Line 166-170, Page 7).

References:

#1 European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol*, 2018, 69(1):182-236.

The term "recue therapy" as a reason for switch to TAF is a bit simplistic (as this most often refers to emerging treatment resistance and since no concrete HBV resistant mutations have been observed with TDF to date, it is oddly placed). It was mostly due to complications from renal dysfunction and residual HBV DNA replication while undergoing TDF. Please rephrase throughout the manuscript.

Thank you for the critical comment. We agree with the Reviewer that no concrete HBV resistant mutations have been observed with TDF to date, and TAF was switched to due to renal dysfunction and residual HBV DNA replication during TDF treatment. The words "rescue therapy" was used according to the previously published paper "Tenofovir alafenamide as a rescue therapy in a patient with HBV-cirrhosis with a history of Fanconi syndrome and multidrug resistance" by Grossi G. *et al*. (reference #1), then the words "rescue therapy" has been rephrased by "replacement therapy" in the revised manuscript.

References:

#1 Grossi G, Loglio A, Facchetti F, Borghi M, Soffredini R, Galmozzi E, Lunghi G, Gaggar A, Lampertico P. Teofovir alanfenamide as a rescue therapy in a patient with HBV-cirrhosis with a history of Fanconi syndrome and multidrug resistance. *J Hepatol*, 2017; DOI: 10.1016/j.jhep.2017.08.020]

Minor comments:

- ln 4. Running title should be "Incident HCC during TAF".

The running title has been revised according to the Reviewer.

- In 46 and 71. Please add "tenofovir" to "disoproxil fumarate".

In the revised manuscript, "tenofovir" has been added to "disoproxil fumarate".

- In 79. "coexistence of hepatocellular carcinoma" does not apply as a reason for switching to TAF. The authors could reword it to: "HCC monitoring is lacking in patients switching to TAF due to …"

Thank you very much for the suggestions, and we have revised the sentences according to the Reviewer.

- In 90. It seems that ADV was added on? It needs to be explained why LAM was continued despite the patient harboring resistant strains.

Yes, ADV was added on LAM in November 2011. Many studies showed that ADV-resistant mutations emerged in LAM-resistant patients who received ADV monotherapy (reference #1 and 2). The add-on strategy was recommended in Chinese guidelines for prevention and treatment of CHB (2010 version), and this has been explained in the revised manuscript (Line 111-112, Page 4).

Reference:

#1 Kwon HC, *et al*. Emergence of adefovir-resistant mutants after reversion to YMDD wild-type in lamivudine-resistant patients receiving adefovir monotherapy. *J Gastroenterol Hepatol*, 2009, 24(1):49-54.

#2 Lo CM, et al. Liver transplantation for chronic hepatitis B with lamivudine-resistant YMDD mutant using add-on adefovir dipivoxil plus lamivudine. *Liver Transpl*, 2005,11(7):807-13.

- In 94. Why was ADV, with known renal toxicities, continued with evidence of renal dysfunction?

The combination therapy of Telbivudine (Ldt) and ADV showed reno-protective effects in CHB patients when compared with other ADV-based combination or single

therapies (reference #1). Moreover, Ldt+ADV therapy showed a significantly higher rate of virologic response than LAM+ADV (reference #2).

References:

#1 Lee M, et al. Telbivudine protects renal function in patients with chronic hepatitis B infection in conjunction with adefovir-based combination therapy**.** *J Viral Hepat*, 2014, 21(12):873-81.

#2 Park H, et al. Efficacy of switching to telbivudine plus adefovir in suboptimal responders to lamivudine plus adefovir. *World J Gastroenterol*, 2013,19(43):7671-9.

- ln 107. There is no evidence in the literature to suspect "TDF resistance". Suggest rewording to "lack of full viral suppression under TDF".

We agree with the Reviewer that "suspected TDF resistance" is not critical, and then "lack of full viral suppression under TDF" was revised according to the Reviewer.

- ln 118. Again, the reason for switch was not due to liver cirrhosis (as presented here). Suggest deleting.

We agree with the Reviewer, and the words "HBV related liver cirrhosis" was deleted in the revised manuscript.

- ln 127. "TDV" should be replaced with "TDF". - ln 133-4.

We are sorry for the spelling mistake, and "TDF" was corrected.

The evidence for lack of renal issues during TAF suggests no need to add LDT. Please delete the sentence "The combination of LDT and TAF…"

We have deleted this sentence in the revised manuscript according to the Reviewer's

helpful suggestion.

Reviewer 2:

In this report, Lu et al. provide a succinct account on the development of hepatocellular carcinoma in a Chinese patient infected with hepatitis B virus. The case illustrates a situation where switching antiviral therapies seems to have little effect on disease progression despite suppression of viral replication. In my opinion, the manuscript is weak due to several reasons:

(1) Authors concentrate on the evolution of kidney function, but there is little information on the evolution of hepatic function (only ALT values are monitored).

Thank you for the critical comment. The present case report indicated that TAF can be a rescue therapy in patients with coexistence of renal dysfunction and multi-drug resistance. Moreover, a potent NA which can maintain HBV suppression, reduces but does not eliminate the risk of HCC development, so the surveillance for HCC should be continued during TAF treatment. Considering laboratory tests showed normal aspartate aminotransferase (AST, <40U/L), total bilirubin (<17.1 μmol/L) and albumin (>35g/L) at admission, we concentrated parameters of kidney function and levels of HBV DNA. These were explained in the revised manuscript (Line 101-105, Page 4).

(2) How sensitive was the viral load test used? What does it mean undetectable? Is it less than 1 log10IU/ml? Is there any information of the HBV genotype infecting the patient? Was it a commonly found strain?

Thank you for the professional comment. HBV DNA was detected with a Cobas TaqMan Test (lower limit of detection, 20 IU/ml), and this has been described in the

revised manuscript. Although the HBV genotype was not detected, a commonly found strain with rtL180M, rtM204V and rtT184A mutations was identified.

(3) Authors should define abbreviations when cited for the first time: HCC in the abstract; eGFR in the text. The recommended way to report the estimated glomerular filtration rate is in "mL/min/1.73 m²" (https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators/mdrd-adults-conventional-units). Are reported values reasonable for the patient? This should be discussed carefully.

The abbreviations have been corrected in the revised manuscript. Due to a lack of reliable biomarkers for evaluating the kidney function, eGFR is the most widely used parameter in clinical practice. This has been discussed in the Discussion section (Line 156-157, Page 6).

(4) Please use μmol/L instead of umol/L throughout the text: e.g. at lines 93 & 95

μmol/L has been corrected throughout the text.

(5) Please separate values and units. It should read 117 U/L instead of 117U/L. Make appropriate changes at lines 84, 104 and in the Figure (CK value and Cr(μmol/L))

Values and units have been separated throughout the text.

(6) Abstract, lines 50-51 should read: "… we describe a clinical case concerning a 60-year-old individual suffering liver cirrhosis and renal dysfunction, and infected multidrug-resistant HBV. When failing treatment with TDF, he received TAF as rescue therapy."

We agree with the Reviewer, and the sentence has been revised.

(7) Page 4, line 86: “took valsartan capsule” (please indicate the precise doses and medication received)

The precise doses and pharma have been added in the revised manuscript.

(8) Page 4, line 94: “Lam was switched…” This sounds incorrect (at some point I thought Lam was the name of the patient. Probably, authors wanted to write: “Then, the patient was treated with LDT and ADV, instead of LAM and ADV, due to the superior nephron-protective effect of LDT.”

Thank you for the critical comment. The sentence has been corrected according to the Reviewer.

Reviewer 3:

In this case report Tenofovir Alafenamide was evaluated in old patient with multidrug resistance and renal dysfunction. Authors have presented this case well. Sincerely.

Thank you very much for the Reviewer’s kindly comments.