Reviewer 1 : This is an excellently written paper, which represents a case report on previously non-identified resistance of CHB patient to Tenofovir. This negative result seemed to be associated to some unusual mutations, which the authors interpreted as the treatment-induced. The only thing, which is not quite clear is when they mentioned that there was no HBe seroconversion, did they mean that the patient did not develop anti-HBe response or that he still had HBe persistence after the treatment with both nucleoside analogues? This is important because HBe persistence indicates that after the treatment, HBV-infection was still active and thus, the mutations existed at the baseline, but were not treatment-induced. However, if there was no development of anti-HBe in the absence of HBe, it may be related to the lack of protection and a kind of immunodeficiency in this patient, which potentially leads to re-infection (since his mother was also infected and he was in a contact with her). I wonder, whether the patient developed anti-HBs after successful completion of the treatment course? It will be useful to address these issues in the Discussion

Answer : Thank you for your comment. The patient had still HBeAg although he had taken TDF for 43 months. This might be associated with vertical transmission. He had still HBeAg after entecavir treatment. It was because he had taken it for only 4 months. I think it was too short to address the successful completion of the treatment course.

Reviewer 2 : How did you confirm that patient is taking his medication? By prescription and refill history? 2. It was stated that "excluded the presence of systemic diseases that might have been able to explain the ineffectiveness of the drug (p.5). What evaluation were performed and what were excluded? 3. Did you do a workup to exclude other cause of a biochemical flare? Did you rule out HDV super-infection? 4. Were patient ever tested for HCV? 5. Since full genome sequencing were done, can simplify the mutation presentation . 6. Was any of the mutation found in this patient associated with ETV resistance? 7. Why was the patient started on ETV 0.5 mg daily? Since he is treatment experienced, should he be on 1mg daily instead?

Answer :

1. How did you confirm that patient is taking his medication? By prescription and refill

history?

- He was vertically transmitted from his mother and he knew the severity of disease and the importance of taking medication. We had prescribed him every 3 months for 43months and he never skipped the hospital visit. After virological breakthrough occurred, we confirmed the drug compliance several times and he denied to skip the medication.

2. It was stated that "excluded the presence of systemic diseases that might have been able to explain the ineffectiveness of the drug (p.5). What evaluation were performed and what were excluded?

- We first thought that immunocompromised state such as AIDS could influence the patient who had been taking TDF. However, we could not find the evidence about that after your review. We will delete the sentence you mentioned.

3. Did you do a workup to exclude other cause of a biochemical flare? Did you rule out HDV super-infection?

- No. We did not workup to exclude other cause of a biochemical flare except test for HCV. We thought that the cause of a biochemical flare was only virological breakthrough because the HBV DNA titer was highly elevated. The test for HDV was not done because we thought HDV super-infection was not possible in the absence of HBV.

4. Were patient ever tested for HCV?

- Yes. The result was negative.

5. Since full genome sequencing were done, can simplify the mutation presentation.

- Full genome sequencing revealed the mutation of rtY9H, rtL91I, rtS106C, rtS106G, rtT118C, rtT118G, rtQ267L, rtI269L, rtA317S, rtK333Q, and rtN337H.

6. Was any of the mutation found in this patient associated with ETV resistance?

- The mutation associated with ETV resistance was not found.

7. Why was the patient started on ETV 0.5 mg daily? Since he is treatment experienced, should he be on 1mg daily instead?

- ETV 1mg was being recommended in lamivudine, adefovir resistance. However, the dose of ETV in TDF resistance was not well known because of its rarity and insurance in Korea had not

permitted ETV 1mg.