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World Journal of Gastroenterology

Dear Editors,

We thank *World Journal of Gastroenterology* for considering our manuscript entitled, "Autoimmune hepatitis in HIV-infected patients: a case series and review of the literature" by Chaiteerakij et al. to be published in *World Journal of Gastroenterology* (Number ID: 03664977).

We have reviewed the comments and have considered them carefully. The point-by-point responses to reviewers' and editors' comments are below:

Reviewer 1
The authors present a case series of patients with HIV and raised liver function tests from Thailand, who eventually were diagnosed with AIH. The work reads well, it is well organised and clear. The text is coherent and clinically meaningful. References are well chosen.

Minor remarks:
1. It would be worth to mention the full work up that has been done for differential diagnosis of raised transaminases, including viral hepatitis serology/viremias (especially hepatitis E status) and rare causes of liver damage -on top of that, did authors include drug-induced liver injury as possible diagnostic hypothesis?

Response: We thank the reviewer for this suggestion. We have added sentences mentioning about laboratory investigations that were done to work up the causes of abnormal liver function tests, including viral hepatitis A, B, C and E infection, thyroid dysfunction, hemochromatosis, Wilson's disease and nonalcoholic steatohepatitis under the section Laboratory examinations on page 8-9 as follows:

"Because viral hepatitis infection, including viral hepatitis A, B, C and E (HAV, HBV, HCV and HEV), is one of the common causes of abnormal liver chemistry, blood tests for hepatitis B surface antigen (HBsAg), antibody to HAV, HCV and HEV were performed. All 13 patients were tested for HBsAg and anti-HCV antibody. One patient was positive for HBsAg and another patient was positive for Anti-HCV antibody, however, both patients had undetectable HBV DNA and HCV RNA viral load at AIH presentation. There were 7 (54%) and 7 (54%) of patients who were tested for anti-HAV IgM and anti-HEV IgM antibody. All were negative for the tests.

Other blood tests to investigate the possible causes of abnormal liver chemistry included thyroid function test (n=5), iron studies (n=5), ceruloplasmin level (n=1) and controlled attenuation parameter by FibroScan® (n=7). The results were all negative."

We also included alcoholic hepatitis and drug-induced liver injury as differential diagnoses of abnormal liver function tests in our patient cohort. We have added a sentence to describe about these 2 possible causes of abnormal liver function tests under the Further diagnosis work-up Section on page 9 as follows:

"History of alcohol consumption as well as medication and herbal use was thoroughly reviewed to exclude alcoholic hepatitis and drug-induced liver injury as possible causes of abnormal liver chemistry."

2. It is interesting to notice that no one developed a flare, which is unusual in AIH.

Response: We apologize for providing the unclear information in the previously submitted manuscript. Indeed, of the total of 13 patients, one (patient number 1 in Table 3) developed a minor flare as described in the Outcome and follow-up section on page 10. The clinical course of this particular patient is shown in the below table. However, no patient had a disease relapse as the immunosuppressive drugs had never been discontinued in all patients.

	At AIH diagnosis	Follow up visit				
		Month 3	Month 6	Month 10	Month 16	Month 19
Lab						
AST (U/L)	121	50	36	28	71	22
ALT (U/L)	263	93	54	35	100	33
IgG (mg/dL)	2930	2130	N/A	1452	2254	1540
Treatment						
Prednisolone (mg/d)	30 mg/d for 2 weeks followed by 20 mg/d for 4 weeks and 15 mg/d afterwards	10	5	2.5	Increased the dose to 15 mg/d for 2 weeks, followed by 10 mg/days	5
Azathioprine (mg/d)	0	50	50	50	50	50

We have added sentences to provide additional information on the clinical course of this patient in the Outcome and follow-up section on page 10 as follows:

"One patient experienced a minor flare when the dose of steroid was tapered. At the time of AIH diagnosis, AST and ALT levels were 121 and 263 U/L, respectively, with IgG level of 2930 mg/dL. He was initially treated with prednisolone 30 mg/day for 2 weeks, followed by 20 mg/day for 4 weeks and 15 mg/day for 6 weeks. Three months after treatment initiation, AST and ALT levels decreased to 50 and 93 U/L, respectively, with a declined level of IgG to 2130 mg/dL. Azathioprine 50 mg daily was therefore added with gradual reduction of prednisolone dosage to 10 mg, 5 and 2.5 mg/day during the next 7 month period. At month 16 after therapy, AST and ALT levels increased to 71 and 100 U/L, respectively, with rising IgG of 2254 mg/dL. Prednisolone was therefore increased to 15 mg/day for 2 weeks, followed by 10 mg/days for 10 weeks, while the dose of azathioprine remained at 50 mg daily. Three months later, AST and ALT levels declined to normal limits (22 and 33 U/L) as well as IgG returned to normal level (1540 mg/dL). The patient was therefore prescribed a low dose prednisolone (5 mg daily) and azathioprine (50 mg daily) as a maintenance therapy to prevent relapse.

The immunosuppressive drugs had never been discontinued in all patients, thus, none of the patients had disease relapse"

3. This could be a merit of good treatment protocols but again it is necessary that authors reveal better how they assessed these patients

Response: We thank the reviewer for this comment. We have added sentences to describe how the patients were assessed for treatment response in the Outcome and Follow-up section on page 10 as follows:

“Liver chemistry was monitored every 2 week during the first month after treatment initiation and every 1-4 months afterwards depending on clinical outcome and the primary physician’s judgement. None of patients performed repeat liver biopsy.”

Reviewer 2

This manuscript describes 13 HIV-infected patients who developed autoimmune hepatitis. The paper is well written. I should like to suggest some minor changes and additions:

1. In the section "Case Summary" the actual status of HIV-infection must be added (CD4 count, viral load, stable HIV suppression).

Response: Thanks for this suggestion. The actual status of HIV infection has been added in the Case Summary section on page 4 as follows:

“We present 13 HIV-infected patients (5 males and 8 females) who developed autoimmune hepatitis (AIH) after their immune status was restored, i.e. all patients had stable viral suppression with undetectable HIV viral loads, and median CD4+ counts of 557 cells/x10^6 L.”

2. It is probable that the emergence of AIH in HIV-infected persons is something like an IRIS. However, it is striking that the presenting symptoms - aminotransferases, jaundice - arose very late in the course of the disease. How was the immune status of patients during the last years? Stable? Or some change in ART which may have induced a rapid improvement of immune status?

Response: Of the total of 13 patients, 7 patients had available data on annual CD4 count during the past 2-3 years. Among these 7 patients, 5 patients had an increased trend of CD4 counts while 2 patients had a slight decline in CD4 counts over years, implying that some patients had improved but some had worsening immune status during the last years prior to AIH development. Regarding the change in ART regimen, 9 patients had taken the current ART regimen for at least 3 years; while 2 patients had been switched to the current ART regimen for 1 year with improvement in CD4 counts after switching (669 to 798 and 377 to 557 cells/x10^6 L) and 2 patients had been switched to the current ART regimen for 6 months, with unavailable data on CD4 counts before switching. All 13 patients had undetectable HIV viral load at AIH presentation.

Due to the limited number of cases and limited information in our cohort, it is difficult to draw a conclusion whether rapid improvement of immune status induces AIH development in our patients.

To provide information on immune status of patients, we have added the duration of current ART regimen, duration of undetectable HIV viral load and CD4 counts in 2 years and 1 year ago and at AIH presentation in Table 2 on page 29 accordingly.

3. The authors should indicate levels of alkaline phosphatase, even if the enzyme is not more included in the simplified AIH scoring system.

Response: We thank the reviewer for this suggestion. Level of alkaline phosphatase of each patient has been added to the Table 2 on page 29 accordingly.

4. How was AIH score?

Response: The simplified AIH score was used in this report. We have added simplified AIH score in the Table 2. There were 8, 1 and 4 patients who had the AIH score of 7 (definite AIH), 6 (probable AIH) and 5 (possible AIH), respectively. Of the four patients who had the AIH score of 5, three patients were treated at our hospital. Although they have the AIH score of less than 6, other possible causes of abnormal liver chemistry were excluded and the liver chemistry improved after immunosuppressive therapy, suggesting that AIH is likely the cause of abnormal

liver function tests. All 3 patients remained on immunosuppressive drug with good response. The last patient was initiated treatment and followed-up at the primary hospital, we therefore did not have information on clinical course after treatment.

5. Can one identify genetic risk factors of AIH in HIV patients? HLA testing done?

Response: Human leukocyte antigens have been identified as genetic risk factors of AIH. HLA-DR3 and HLA-DR4 are known to be susceptible genes in Caucasian and Japanese populations, respectively. However, genetic polymorphisms as risk factors for AIH specifically for HIV populations haven't yet been identified.

We thank the reviewer for this insightful question. Unfortunately, we did not perform HLA testing in our patients. We would consider doing this as a future project.

We have added sentences to describe about genetic risk factors of AIH in the Discussion section on page 12 as follows:

"Human leukocyte antigens have been identified as genetic risk factors of AIH. HLA-DR3 and HLA-DR4 are known to be susceptible genes in Caucasian and Japanese populations, respectively. However, genetic polymorphisms as risk factors for AIH specifically for HIV populations haven't yet been identified."

We believe that our responses and manuscript modifications will prove satisfactory upon review. We thank again the editors and reviewers for their insightful comments. .

Sincerely,

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