Dear Chief Editor:

We appreciate the comments from the reviewers. Below are the point-to-point response to the comments.

Reviewer 1: A well written comprehensive review on hepatitis B reactivation in patients requiring chemotherapy.

General comments: It would be helpful to have a conclusion at the end of each immunosuppressive medication/disease state section to summarize the recommendations with regards to HBV prophylactic therapy. eg: HCC: Due to high incidence of HBVr, it is recommended to initiate antiviral therapy in all patients with HBV related HCC undergoing chemoradiation, locoregional or systemic therapy.

Reply to comments: We thank the reviewer for the instructive comments. We have added a conclusion at the end of each immunosuppressive medication/disease state section as the suggestion.

1. Hematologic Malignancies: We recommend antiviral prophylaxis in HBsAg-positive patients from 1 week before starting immunosuppressive agents and until 12 months after discontinuation of the agents. We also recommend that HBsAg-negative/anti-HBc–positive patients on drugs that target B lymphocytes such as rituximab should be given antiviral prophylaxis.
2. Solid Tumors: We recommend antiviral prophylaxis in HBsAg-positive patients from 1 week before starting immunosuppressive agents until 12 months after discontinuation of the agents. At present there are insufficient data to recommend antiviral prophylaxis in HBsAg-negative/anti-HBc–positive patients.
3. HCC: Due to high incidence of HBVr, we recommend to initiate antiviral therapy in all patients with HBV related HCC undergoing chemoradiation, locoregional or systemic therapy.
4. HSCT: We recommend prophylactic antiviral therapy in patients receiving high-risk therapies such as anti-CD20 antibodies or HSCT recipients.
5. Rheumatologic diseases: We recommend that HBsAg-negative, anti-HBc–positive patients with rheumatological conditions receiving biological therapies and patients with psoriasis treated with biologicals or conventional immunosuppressive therapies could be monitored without anti-HBV prophylaxis (Hepatology 2018;67:1560).
6. Inflammatory bowel disease: We recommend that HBsAg-negative, anti-HBc–positive patients with inflammatory bowel disease treated with TNF inhibitors, biologicals or conventional immunosuppressive therapies

could be monitored without anti-HBV prophylaxis.

Specific comments:

1. Page 6: “In patients with resolved HBV infection, 27 (8.2%) developed HBVr after chemotherapy [32]. Of the patients without prophylactic nucleos(t)ide therapy, 10.8% had HBVr while only 2.1% patients had HBVr if prophylactic nucleos(t)ides were given [32]” Please elaborate on the study (reference 32). Patient population, total N, type of immunosuppression received, and total number who received prophylaxis and proportion in each group with HBVr.

   Reply to comments:

   We have elaborate on the study in Page 6 as follows.

   In a multicenter, randomized, phase 3 study of 326 diffuse large B-cell lymphoma or follicular lymphoma patients with resolved HBV infection, 27 (8.2%) had HBVr which occurred at a median of 125 days after the first dose of obinutuzumab or rituximab immunochemotherapy. Twenty-five of 232 patients (10.8%) without prophylactic nucleos(t)ides had HBVr while only 2 of 94 patients (2.1%) with prophylactic nucleos(t)ides had HBVr [32].

2. Page 7 “corticosteroids at a daily dose of ≥ 20 mg for ≥ 4 weeks” Please state “dosage equivalent to prednisone 20mg daily” ” Because HBsAg-negative patients with NHL frequently present a direct HBV infection of lymphocytes, chronic antigenic stimulation and associated B-cell proliferation [22].” This is verbatim from reference 22 which is a review article itself. It is a vague sentence and needs to be clarified. Please refer to the original article cited in reference 22 and clarify.

   Reply to comments:

   We clarify the sentence and refer to the original article in Page 7 as follows.

   Moderate risk: HBsAg-positive/anti-HBc–positive patients treated with low-dose (<10 mg prednisone daily or equivalent) corticosteroids for duration of 4 weeks. HBsAg-negative/anti-HBc–positive patients treated with moderate-dose (10–20 mg prednisone daily or equivalent) or high-dose (>20 mg prednisone daily or equivalent) corticosteroids daily for 4 weeks (Gastroenterology 2015; 148:215).

3. Page 9 – under Rheumatologic diseases The introduction of tumor necrosis factor α (TNF-α) inhibitors and other biological agents increase the risk of HBVr in these patients [49].” Please quantify the increased risk – by how much? What is the treatment recommendation for this group?

   Reply to comments:

No risk of HBVr while received tumor necrosis factor α (TNF-α) inhibitors was presented in this article for the reference [49]. Therefore, we modify this sentence and the reference as follows.

Tumor necrosis factor α (TNF-α) inhibitors (eg, etanercept, infliximab, and adalimumab) are associated with HBVr when used in patients with Crohn disease, rheumatoid arthritis, and psoriasis. Patients who are HBsAg-positive may have risk of reactivation of around 1% to 10%. On the contrary, the reactivation risk is less common in HBsAg-negative, anti-HBc positive patients (around 1%) [49]. Therefore, we recommend that HBV prophylaxis may not be indicated in HBsAg-negative/anti-HBc-positive patients while they could be monitored for hepatic biochemical flare during immunosuppression.

4. Page 10 Please define “pre-emptive therapy” - at what point should one initiate therapy? How often to monitor, etc . . . You need to clearly state the difference between primary prophylaxis (initiate therapy before chemotherapy) and pre-emptive therapy. Please clarify the section under “Moderate-risk patients (1-10%)” In whom would you recommend pre-emptive therapy and who should get prophylactic therapy?

Reply to comments:

We clarify the statement in Page 10 as follows.

Pre-emptive therapy is defined as antiviral therapy which is initiated when serum HBV DNA or ALT levels are elevated but before symptomatic manifestation of hepatitis or liver failure. Primary prophylaxis therapy is defined as antiviral therapy which is started prior to or at the same time as the initiation of immunosuppressive therapy and before any elevations in HBV DNA or ALT levels (Nat Rev Gastroenterol Hepatol 2014;11: 209). In HBsAg-negative and anti-HBc positive subjects with moderate (<10%) or low (<1%) risk of HBVr, pre-emptive therapy, instead of prophylactic therapy, is generally recommended (J Hepatol 2017;67:370). Pre-emptive therapy is based on monitoring HBsAg and/or HBV DNA at 1 to 3-month intervals during and after immunosuppression, and starting ETV, TDF or TAF treatment in case of detectable HBV DNA or HBsAg seroreversion (J Hepatol 2017;67:370).

5. Page 10 “Given the fact that screening for HBV before chemotherapy and immunosuppressive therapy with prophylactic antiviral agents could significantly decrease the occurrence of HBVr, the screening rates remain relatively low in non-HBV endemic countries such as the United States (17%) and Canada (14% to 31%), as well as in China (17%), one of the HBV endemic countries [63-65]”

Need to clarify this sentence. The way it reads now it appears that China is a non-endemic country.

Reply to comments:

We revise this sentence as follows.

Given the fact that screening for HBV before chemotherapy and immunosuppressive therapy with prophylactic antiviral agents could significantly decrease the occurrence of HBVr, the screening rates remain relatively low in non-HBV endemic countries such as the United States (17%) and Canada (14% to 31%) [63-65]"

6. Page 11 "A computerized order entry–based alert system (e-REMINDER) and a therapeutic control system (e-CONTROL) achieved . . ." Please provide more information on this study. Where was this program? What was the total N? Study design etc . . .

Reply to comments:

We revise the statement about the study as follows.

A retrospective cohort study from Taiwan which included 2512 cancer patients receiving chemotherapy found that a computerized order entry–based alert system (e-REMINDER) and a therapeutic control system (e-CONTROL) achieved a very high pre-chemotherapy HBV screening rate (99.3%) and a high antiviral agents prophylactic rate (95.8%) without any event of severe or acute HBVr (Fig. 2) [66].

7. Table 2: Please note that anti-CD20 antibodies is synonymous with B-cell depleting agents. Both terms are used in the table.

Reply to comments:

The term anti-CD20 antibodies is used in Table 2 as suggestion.

8. Fig 1. HBsAg- negative and anti-HBc positive pts who receive high risk IMS – can Lam be used in this population? Do they need to start therapy 7 days in advance? Can you provide a reference for the 7 day advanced treatment initiation? "Monitor HBsAg, HBV DNA levels and ALT every 3-6 months until after completing anti-HBV therapy for 12 months" Is this monitoring frequency reasonable for all levels of risk? ie q6months in a pt with moderate risk of HBVr?

Reply to comments:

A. In fact, lamivudine is associated with a high rate of drug resistance when used beyond 1 year. Due to the fact that cancer chemotherapy regimens often fall short of 1 year and lamivudine resistance is uncommon in patients before 6 to 9 months of therapy

(Gastroenterology 2015;148:221), lamivudine could be used as first-line therapy for prophylaxis with short-term immunosuppressive therapy in the HBsAg-negative/anti-HBc–positive patients. This offers the advantages of reduced cost and broad availability worldwide.

B. Regardless of baseline serum HBV-DNA level, prophylactic antiviral therapy should be administered to patients with chronic hepatitis B before (i.e., most often in the literature, antivirals were given 7 days before) the onset of anticancer therapy or a finite course of immunosuppressive therapy (Hepatology 2018;67:1578).

C. The most commonly studied and recommended duration of prophylactic antiviral therapy is 6-12 months after discontinuation of anticancer therapy or immunosuppression. Reactivation beyond 12 months has been reported, so further monitoring should be considered, particularly for patients who received anti-CD20 antibody therapy. For patients being monitored without prophylaxis, HBV-DNA levels should be obtained every 1-3 months. (Hepatology 2018;67:1579).
We revise the statement of monitoring as follows.
Monitor HBsAg, HBV DNA levels and ALT every 3 months until after completing anti-HBV therapy for 12 months

Reviewer 2: Good overall review on this topic. Good effort in developing the algorithm, but it did not include all the factors needed to consider before making a decision on starting on prophylaxis anti-viral. E.g. for those with HBsAg + and anti-HBc, those with normal ALT and HBV DNA 2000, it seems like treatment is recommended without considering the potency/duration of immunosuppression. Individuals needing a low dose of steroids for very short term or methotrexate might not necessarily need prophylaxis if they have no fibrosis, low HBV DNA and ALT. In the table, I would suggest specifying what "general immunosuppressants" in the low risk group, giving some examples will help the readers.

Reply to comments:

1. We agree that in HBsAg + and anti-HBc patients with normal ALT and HBV DNA 2000, treatment is recommended without considering the potency/duration of immunosuppression and the Figure 1 is modified. In the Figure 1, “Individuals needing a low dose of steroids for very short term or methotrexate might not necessarily need prophylaxis” is listed as a new column (HBV DNA < 2000 IU/mL and normal ALT without liver fibrosis) of HBsAg-positive and anti-HBc-positive patients.

2. In Table 1, azathioprine, 6-mercaptopurine, and methotrexate are listed in the low risk group as general immunosuppressants.

   Thanks for the reviewer's valuable and constructive comments!