Peer Review File

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Reviewer A

The authors are examining cost-effectiveness of treatment of HBV in a selected patient group. The aims of the study appear valuable from an efficiency perspective, though I cannot comment on the clinical perspective.

As a general comment, I found it challenging to exactly understand the clinical options assessed - whether it was mostly the combination treatment, a combination treatment of long duration, or in a specific subgroup of patients. It would help to make the clinical stratification very clear, and perhaps provide additional details of the supporting clinical (observational) evidence in the background.

We are grateful to you for pointing out this shortcoming in our paper. Accordingly, we have modified the background part and supplemented related evidence as a reference.

Several studies showed that a longer period of PegIFN α-based treatment of more than 48 weeks and combination therapy with NA+PegIFN was likely to improve the HBsAg clearance rate. Based on these data references and our clinical practice, we explore this strategy on efficacy and cost-effectiveness. Please see Page 5-6, Line 108-113.

My other general comment is that the manuscript needs a good edit for language, many phrases can be grammatically and semantically improved. I would recommend the authors to collaborate with a good English-native technical/scientific writer, to ensure all explanations are clearly worded.

Thank you for your comments about this shortage. We have revised the whole manuscript language and seek advice from an English-native scientific writer. You can refer to the revised manuscript.

Other specific comments are provided below for the authors' and editors' consideration:

• Discount rate of 5% pa should be justified or cited

Thank you for your suggestion. We have added the reference to state the discount rate in the revised version. Please see Page 10, Line 209-210, and reference in Page 19,

Line 432-433.

• There is no statement on the perspective of the analysis – it appears to be "healthcare" or "payer", but the authors do not state. The CHEERS checklist in appendix suggests that it is, but the pages/lines referenced do not contain that information.
Really thank you for your valuable suggestion. This analysis was from the perspective of health care and patients. We have supplemented the content about this information. Please see Page 9, Line 192-193.

• The intervention and comparator (lines 152-55) are not very clearly described, which makes it hard to grasp the alternatives considered in the model. The strategies appear to be summarised in table 4.
We are appreciated for your pointing this part. The comparator is traditional NA monotherapy (Entecavir 0.5 mg per day or Tenofovir disoproxil 300 mg per day). We have modified the wording on Page 7, Line 146-148. And Table 4 also has been updated accordingly.

• Relatedly, it's difficult to understand which of the options is the "comparator" and which is the "intervention" – "lowest lifetime cost treatment was considered as the reference therapy" could be replaced with which one of the options it is: Monotherapy or combination therapy
Thank you for this comment. Here, traditional NA monotherapy was the comparator, combination therapy was intervention, and combination therapy was considered the reference therapy. Please see Page 7, Line 146-148.

• Consider whether a normal distribution is most appropriate for costs in the probabilistic analysis. Frequently, costs are skewed and a gamma distribution is applied. However, the authors can elaborate on their choice of distribution and ensure it is consistent with their data.
We are grateful to Reviewer A for pointing out this shortcoming in our manuscript. As a result, we have re-run this data and applied a gamma distribution for costs, updated our results in the main text of Page 11, Line 233-235, and updated Figure 3 as well.

• References appear to be missing in table 2, there is also a fourth column with numbers (438, 439), it's not clear what these are
Thanks a lot for your comment, in Table 2 showed mean utility estimates for chronic hepatitis B-related health states, and the reference was presented in the full text. Please see Page 9, Line 192-195. And a column with numbers has been removed.

Please see Table 2 in the revised version.

• Table 3: Some explanatory footnotes would help to understand the disease-state costs. For example, it's unclear why costs for HBsAg loss and chronic HBV are identical. It would help to specify, at least, what is the perspective of these costs – e.g. commodities, medical staff/tariffs, etc. There is a decimal error in costs for DCC.
Really thank you for your suggestion. The disease-state costs are including the cost of annual medical management cost, laboratory testing, and examinations, which have been added in Table 3 with a note. And the cost of DCC is a decimal indeed, have modified it accordingly. Please see the updated Table 3.

• Table 4: It's unclear why there are NA values in the combination therapy line, while there are values in the subgroups stratified below. Also why the incremental costs are zero in combination therapy and NA in the subgroups below. This may be related to the choice of comparator, but it's not clear
Thanks for your suggestion. Table 4 presented two kinds of treatment strategies, NA monotherapy as a comparator and combination therapy as an intervention. Within combination therapy, also presented three sub-groups cost-effective results. In this Markov model, combination therapy as reference therapy, so the incremental cost was zero. We have updated Table 4 for a much easier understanding. Please refer to the updated Table 4.

• There appears to be a problem with fig. 3. Logically, the % iterations which are cost-effective should not decrease with a higher WTP. Also in the text, this figure is referred to as supplementary materials, instead of figure 3.
We are thankful for your comments. We have updated Fig 3 with more straightforward presentation.
And supplementary material was the typo, shown in Figure 3, instead of supplement materials. We have revised the wording. Please see Page 12, Line 260-262.

Reviewer B
This study described the economic impacts of treating a highly selected cohort of people with HBeAg negative chronic hepatitis B and HBsAg<=1000IU/ml, using 1) combined NAs with Peg-IFNa for 96 weeks or 2) the NAs monotherapy strategy. My main comments are:
1. The authors need to provide robust evidence of clinical benefits of proposed strategy over comparator, as most parameters suggesting a higher rate of HBsAg loss among this population using the proposed strategy was from one single study.
We are grateful to you for pointing out this shortcoming in our paper. Accordingly, we

have modified the background part and supplemented related evidence as a reference. Several studies showed that a longer period of PegIFNα-based treatment of more than 48 weeks and combination therapy with NA+PegIFN was likely to improve the HBsAg clearance rate. Based on these data references and our clinical practice, we explore this strategy on efficacy and cost-effectiveness. Please see Page 5-6, Line 105-122.

2. More background information is needed on why the authors choose "NAs monotherapy strategy" as the comparator. Why not comparing the proposed strategy to current treatment protocol, because part of the population with HBeAg negative chronic hepatitis B might not require treatment as per current clinical guidelines.
Thanks you for this comment, here traditional NA monotherapy was the comparator, and combination therapy was an intervention, and combination therapy was considered as the reference therapy. Please see Page 7, Line 145-148. As you mentioned the population with HBeAg negative CHB not require treatment, who are inactive HBV infection with natural HBVDNA negative. While in our research, we targeted the population of HBeAg negative patient, who are the chronic active CHB with HBeAg negative under NA treatment. For this population, the international guidelines recommend NA with long-term consolidation treatment until HBsAg loss, after HBV-DNA turns negative for patients with chronic hepatitis B e-antigen (HBeAg) negative chronic hepatitis B. However the proportion of HBsAg loss from long-term use of NAs is very low, and the risk of drug resistance, also makes the treatment limited for this group. Based on these data references and our clinical practice, we explore this strategy on efficacy and cost-effectiveness. You can refer to the revised content on Page 5, Line 100-104.

3. All parameters for each strategy need to reflect the population selected, for example, transition rates between different disease states should be rates among people with HBeAg negative CHB with HBsAg<=1000IU/ml. If limited data on these parameters, adjustment from sourced parameters is needed.
Thanks a lot for your suggestion. In our research, we refer to published data as transition rate, also adjusted the transition rate about different sub-group into HBsAg loss, given very limited data to present different subgroup to show other disease state transition, e.g., to CC, to DCC, to HCC, so hereby use same data. Details information, please refer to the updated Table 1.

4. Results of ICER need to be added in both abstract and main text.
We are very grateful to you for pointing out this one. We have been added ICER in

Table 4, and in the main text accordingly. Please see the updated Table 4, abstract on Page 3, Line 73-74 and the main text on Page 11, Line 242-244.

5. Discussion needs to focus on the findings of the cost-effectiveness and their implications instead of explaining why the proposed strategy was chosen. More discussion is needed on how the finding would contribute to clinical decision making.
We are thankful to you for raising this comment. Based on your suggestion, we have revised the discussion point. Please see the discussion part on Page 12-14, Line 265-316.

Please see below some detailed comments.
Abstract
• Missing results on ICER in results section.
Really thanks for your comment. ICER has been added in the abstract result part as well as in the main text result part. Please see Page 3, Line 73-74 and Page 11, Line 242-244.

• In the conclusion "This observation provides alternative treatment option for HBeAg negative patients to achieve higher functional cure rate in clinical practice."- I don't think cost-effectiveness data could suggest treatment options in clinical practice.
Thank you so much for this comment. We revised the abstract conclusion part based on your suggestion. Please refer to Page 4, Line 78-82.

Main texts
• Line 122-124, "For hepatitis B e antigen (HBeAg) negative CHB, NA with long-term consolidation treatment as recommended even until HBsAg loss in the national guideline, which makes the treatment limitation for HBeAg negative CHB". This sentenece does not make sense to me.
Thanks for your comment. I agree with your point. We have re-written this part. The international guidelines recommend NA with long-term consolidation treatment until HBsAg loss, after HBV-DNA turns negative for patients with chronic hepatitis B e-antigen (HBeAg) negative chronic hepatitis B. However the proportion of HBsAg loss from long-term use of NAs is very low, and the risk of drug resistance, also makes the treatment limited for this group. Details, please see Page 5, Line 100-104.

• Line 126, please define "clinical cure" or be consistent with terms used (functional cure/ clinical cure/ HBsAg loss/ HBsAg clearance/ HBsAg seroconversion).
We are thankful for your comment. We have modified related wording and kept it consistent in the whole manuscript on functional cure and HBsAg loss. You can refer

to the updated full paper. About HBsAg, seroconversion is another transition statement. Hence still keep the seroconversion wording.

• Line 126-134, Reference 8-12 were studies suggesting clinical benefits of switching NAs to PegIFN alfa-2a among HBeAg positive patients. More relevant data is needed to support the clinical benefits of "NA and Peg-IFNa combination with extended-duration of 96 weeks" in HBeAg negative patients. Also, it would be helpful to clearly state the comparator, why the authors choose them instead of current agreed treatment protocol (if it's different from the current treatment protocol)
Thanks for your suggestion. We have re-checked the published data and added some references into the background and discussion parts to supplement the combination therapy strategy. NA monotherapy as the comparator treatment, NAs have been the SOC treatment and listed as the reimbursement drug. Please see the update part on Page 5-6, Line 108-116.

• Line 147-150, as the HBsAg clearance rate of 6.7%, 31.8%, and 67.% in subgroups of HBeAg negative population are key parameters in your model, you might consider add references. Also, is there a range for these parameters or if any range was used for sensitive analysis.
Thanks for your comment. We have checked the original reference and found there was not more description about the range. We added the reference hereby. Please see the updated version on Page 6-7, Line 132-143.

• Line 174, if you have 48 weeks as a cycle, have you adjusted the parameters for each cycle? (For example, in table 1 you said "annual transition rates of disease states")
We are thankful for your suggestion. We have revised 48 weeks to one year and keep consistent. Please see the details on Page 8, Line 165-171.

• Line 225-235, the section of "Costs of drugs and disease states" reads like methods instead of results.
Thanks for your suggestion. We have moved this part into the methods part. Please refer to the revised methods part on Page 9-10, Line 197-221.

• The discussion of why the authors choose the proposed strategy (first three paragraphs in the discussion) might go to the introduction.
We are grateful to receive this suggestion. We have modified the background part accordingly. Please see the updated version on Page 5-6, Line 94-122.

• Line 287-290 “Based on the Markov model, we also estimated the cumulative lifelong HBsAg loss rate …, which is similar with our clinical practice observation”. This sentence might be an overclaim?

Thanks for your suggestion. This sentence is aimed to present the Markov results about different statement transition is comparable with our clinical observation. Here we revised the sentence. Please refer to the revised methods part on Page 13, Line 290-293.

• More discussion is needed on how the study findings would benefit clinical decision making.

We are grateful to receive this suggestion. We have modified the discussion part accordingly. Please see the updated version on Page 13-14, Line 266-316.

• Table 1, May specify each “CHB” as you were talking about a highly selective subgroups of people with CHB.

Thanks for your suggestion. We have revised Table 1 with clear notes. Please see the updated Table 1 information.

• Table 4. Results of ICER is missing in the table.

We are very grateful to you for pointing out this one. We have been added ICER in Table 4 and in the main text accordingly. Please see the updated Table 4 and main text on Page 11, Line 240-249.

• Figure 2. Please indicate the title/ unit of x axis.

Thank you for your suggestion. We have added the title/unit of the x-axis in Figure 2, and please see the updated Figure 2 about the details.

Language

• I would suggest reducing acronym use unless necessary. For example, you used “HE” (line 89), “FC” (line 120), “DAA” (line 127), “CEAC” (line 220), as these terms were used only once, I don’t feel you need to include their abbreviations. Please check throughout.

Really thank you for your suggestion. We have removed some acronyms use based on your suggestion. Please see the updated full main text.

• This paper might benefit from English editing services.

Thank you for your comments about this shortage. We have revised the whole manuscript language as well as seek advice from an English-native scientific writer. You can refer to the revised manuscript.

Reviewer C

General comments

This paper aims to evaluate the value of HBsAg clearance and health economic analysis of the treatment strategy using NA138 and Peg-IFNa combination with extended-duration for HBeAg negative CHB, which is an important research question. The authors used a Markov model, a well-established methodology to measure lifetime costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness Ratios (ICERs), for cost-effectiveness analysis under the strategy of NA and Peg-IFNa combination with extended-duration in HBeAg negative patients. The authors report that the combination treatment strategy with extended-duration for HBeAg negative selected patient have the advantage to prolong QALY compared to NA monotherapy. and, HBeAg negative CHB with HBsAg ≤10 IU/mL is the most cost-effective population under this strategy. Therefore, I think the paper is interesting but needs refinement in performing additional sensitivity analysis and also language in order to make it easier for the readers.

We are thankful for the positive comments on our research question and overall results. We also appreciate the constructive suggestions given as following.

Major comments

The structure of the Introduction and Research Literature could be improved to motivate the research question better. In particular, in the Introduction section, instead of 3 and bounce between information, the paragraphs can be woven together in a more linear manner. I would suggest having 4 paragraphs. Also, paragraph1 is very short.

The structure of the Materials and Methods also has short paragraphs it could improve.

We appreciate this advice on the background and methods part; based on your suggestion, we have revised the background and methods structure on Page 5-6, Line 90-128, and Page 6-7, Line 132-154.

Did the model include the recurrence of the infection?

We are thankful for your comments about the recurrence of the infection. In our paper, we did not include stability after HBsAg clearance or rescue treatment for recurrent cases, given there were large differences in recurrence rates between different research populations. We have added this point at the discussion limitation part, and please see Page 14-15, Line 318-329.

The manuscript would be improved with additional transparency about model assumptions so that the analysis could be replicated by others.

Thanks for your comments. We developed a Markov model to simulate the long-term disease progression and outcome for HBeAg-negative patients with chronic hepatitis B who were 35 years old, using a treatment strategy of extended-duration combination NA and Peg-IFNa. It included clinical endpoints for eight states among patients with HBeAg-negative chronic hepatitis B: HBsAg clearance, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplantation, post-liver transplantation and hepatitis B-related death. Patients from the initial state (having chronic hepatitis B) could move to other states with a defined transition probability, with death as the final state (see Figure 1). Please see the details on Page 7-8, Line 157-171.

This analysis should include additional sensitivity analyses that reflect different model assumptions. Although one sensitivity analysis was presented in Figure 2, the manuscript would be improved if it presented the results across numerous sensitivity analyses and followed by a discussion of how the results change based on these different assumptions. For example, two-way sensitivity analyses could be done on the top-ranked parameter on the Tornado diagram.

Thanks for your advice. We added two-way sensitivity analyses based on two top-ranked parameters (discount rate and the cost of Chronic hepatitis B status). The x-axis indicates the different discount rates, while the y-axis indicates the different costs of CHB. It is shown that the combination still is cost-effective. Details, please see the supplement material figure, also attached here for your information.

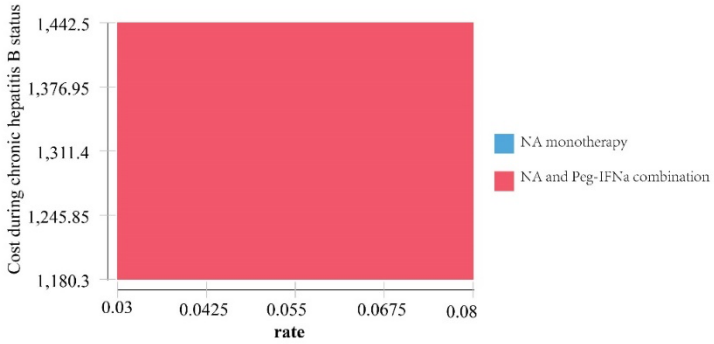

Figure Two-way Sensitivity Analysis of the discount rate and the cost of CHB_NAs

The tornado diagram should be explained better, and the figure legend should be added to the figure. The author may get help from tornado diagram explanation from; Cost-effectiveness of universal and targeted hepatitis C virus screening in the United States. JAMA Network Open, 3(9), e2015756-e2015756.

Thanks for your suggestion. We have updated Tornado diagram based on your advice and also added a figure legend. For details, please see the updated Figure 2 and the Figure 2 legend. Here I also attached for your easier check the update part as follows.

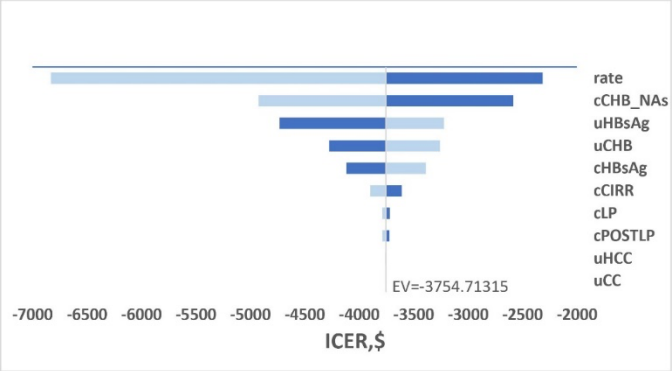

Figure 2 The dark blue portion of each bar represents the low range of the parameter listed on the y-axis, and the light blue portion of the bar represents the high range of the parameter.
When dark blue is on the left and light blue on the right, the ICER increases as the parameter value increases; when light blue is on the left of the baseline, ICER decreases
as the parameter value increases. EV indicates expected value;

The authors stated that in China, about 5%-6% of people are chronically infected with HBV; however, high-risk people (e.g., people who inject drugs, healthcare workers, and people in prisons) may have higher rates. The authors might discuss studies that analyzed the cost-effectiveness intervention for high-risk people in targeted scenarios instead of the total population. For example, Tatar et al. (doi:10.1001/jamanetworkopen.2020.15756) performed a cost-effective analysis on targeted intervention for high-risk people.
Really thank you for this suggestion. We searched the data and found that a published data by Harinder S on the use of monitoring and treatment for HBV high-risk groups can bring pharmacoeconomic benefits and reduce the burden of disease. Our research strategy has not been explored in high-risk groups. Our analysis did not include these kinds of populations. The benefits of combined intervention therapy on HBV high-risk population need to be confirmed by furthermore data. Please see the update about the high-risk population description on Page 14, Line 312-316, and a reference was added on Page 19, Line 444-446.

Additionally, adding targeted intervention scenarios will make the paper more generalizable and more rigorous.
Thank you for this comment, here traditional NA monotherapy was the comparator,

and combination therapy was an intervention, and combination therapy was considered as the reference therapy. Please see Page 7, Line 145-148.